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Dose-Response Issues Concerning Physical Activity and Health: An Evidence-Based Symposium

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PREFACE

Since 1985, a "team" of Canadian exercise scientists have volunteered a considerable amount of time to organize two international conferences that sought to understand the complex interrelationships among physical activity, fitness, and health. For the 1988 (1) and 1992 (2) conferences, based on the research evidence available at the time, a conceptual model and a consensus statement were developed. Then leading exercise scientists presented and interpreted evidence at a conference for scholars and practitioners so that the knowledge could be used in practice or in developing policies. Since the 1992 conference, there has been considerable debate about the issue of "dose-response" (frequency, intensity, duration, type) in relation to the role of physical activity in enhancing health, and in the prevention of disease, disability, and premature death. Consequently, in 1998, the "team," plus a few new members (see below), began to plan a small evidence-based symposium. The purpose of this symposium was to critically examine the evidence concerning the dose-response relationship as it impacts on physical activity and health benefits, and to identify key issues and questions for future research about dose-response issues.

This special issue includes the papers, as revised, that were presented and critiqued at the symposium held October 11–15, 2000, at the Hockley Valley Resort, Ontario, Canada. Each author was invited to participate after a rigorous review identified the most prolific and up-to-date researchers on each of the 24 critical topics that had been identified for discussion by a team of international advisors. A description of the consensus process, including the role of the consensus panel, all of whom were senior international scientists outside the field of exercise science, is included in the "Introduction" by Dr. Claude Bouchard, Program Chair.

By definition, "consensus" implies a collective opinion, a general agreement, and a majority view. Consensus represents both a "process," whereby individuals or groups reach some level of agreement through discussion or debate and an "outcome," which represents, at that time, the best conclusion or interpretation of data based on general agreement by experts. This special issue represents the consensus derived from comprehensive literature reviews and four days of intense and lively debate and discussion.

However, consensus was not reached on a number of dose-response issues. To illustrate, most of the studies on which the evidence was based were completed in Europe or North America. Few, if any, cross-cultural studies have been completed, and, within a country, few studies compare the impact of race, social class, or ethnicity on key input or output variables. Most studies were based on cross-sectional or longitudinal observational studies rather than on randomized control trials. And there appeared to be different levels of interpretation, and different degrees of confidence, in the interpretations. Some of this variation in confidence was related to whether the evidence was based on controlled laboratory/field experimental studies or on population studies. Throughout the symposium, there were heated debates concerning research designs, input and outcome measures, "cut" points, "markers" of activity, and neglected control variables. More specifically, there was considerable discussion among those representing diverse methodological and/or theoretical perspectives as to how physical activity has been, or should be, measured and categorized in laboratory versus population studies. For the Consensus Panel, this debate was both a source of confusion and a learning experience. As well, the Consensus Panel could only consider the papers as they were presented at the symposium, not as revised for this publication.

Although the evidence presented in these papers does represent some degree of consensus, more research and debate remains before unanimity or closure on these topics can be achieved. Thus, we challenge scholars to contribute to the on-going debates by initiating innovative research, by writing critical reviews of the papers in this issue, and by participating in new and multidisciplinary approaches to seeking answers to the remaining questions. Specifically, it is apparent that the field would benefit from increased team research involving those who work from the perspective of both epidemiological and controlled lab/field-based research, especially with respect to the use of theories, concepts, and methods.

A symposium of this magnitude could not be held without the investment of significant human and financial resources. It has been my privilege and challenge to chair a "team" comprised of the following dedicated volunteers: Randy J. Adams (Health Canada); Claude Bouchard (Pennington Biomedical Research Center, Louisiana State University); Cora Craig (Canadian Fitness and Lifestyle Research Institute); Norman Gledhill (York University); Dawn Gledhill (retiree); Veronica Jamnik (York University); Peter Katzmarzyk (York University); Art Quinney (University of Alberta); Art Salmon (ParticipACTION); and Roy Shephard (retiree). Special recognition is due to Norman and Dawn Gledhill for arranging the myriad of details at the symposium site, and to Art Salmon, Chair of the Finance Committee, who led the fund-raising efforts. All of us would like to express gratitude to Drs. Steve Blair, William Haskell, I-Min Lee, and Ralph Paffenbarger, who provided guidance and assistance to the program chair in the final selection of speakers for the symposium.

Major donations were received from both Health Canada and the U.S. Centers for Disease Control and Prevention.

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Proceedings for this symposium held October 11–15, 2000, Ontario, Canada.

This may be the first time that two major federal agencies, in two countries, have cosponsored such a significant scholarly event on the topic of physical activity and health. Sincere thanks are due to the representatives of both agencies for their willingness to support this landmark symposium. Their commitment to the consensus process, and to ensuring that the knowledge from the symposium is shared widely, will be realized in the cohosting of a major conference in Whistler, British Columbia, in September 2001.

In addition to the two major sponsors, we sincerely thank the following organizations for their financial or in-kind support: ParticipACTION; the Canadian Fitness and Lifestyle Research Institute; the Heart and Stroke Foundation of Canada; the Osteoporosis Society of Canada; the Government of Ontario; the American College of Sports Medicine; the Canadian Forces Personnel Support Agency; and, York University. Finally, for their financial contribution to the publication of this special issue, the organizing committee gratefully acknowledges the support of Mars Incorporated and the U.S. Army Medical Research and Materiel Command.

Barry D. McPherson, *Chair*
Symposium Organizing Committee

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Physical activity and health: introduction to the dose-response symposium

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How much physical activity is needed in adults to prevent morbidities, disabilities, and premature death? This is one of the most important questions for all those who have an interest in the topic of physical activity and health and who believe that the promotion of a physically active lifestyle should be the cornerstone of contemporary public health programs. The evolution from performance- and fitness-centered exercise prescriptions toward health-related physical activity recommendations over the last decades had a dramatic influence on this topic. This is best illustrated by the differences in the recommendations contained in the 1978 Position Statement of the ACSM on the issue (1) and in the 1996 Report of the Surgeon General of the U.S. (24).

Recognizing the importance of the issue and the uncertainties concerning the amount of physical activity necessary to generate health benefits, a group of Canadians, among them those who organized the 1988 and 1992 International Conferences on exercise or physical activity and health outcomes (7,8), organized a Symposium entirely devoted to dose-response relationships. The Symposium was held from October 11 to 15, 2000, at Hockley Valley Resort, near Toronto. Participation was by invitation only and 24 experts from six countries were asked to review the evidence for a dose-response relationship between regular physical activity and health outcomes. A Consensus Committee composed of highly respected scientists from other fields was asked to evaluate the evidence and write a Consensus Statement. The Committee was chaired by Dr. Antero Kesaniemi, professor of internal medicine, University of Oulu, Finland. Ample time was set aside for discussion and for the members of the Consensus Committee to ask questions and request clarification on any relevant issues.

ASSESSING THE QUALITY OF THE EVIDENCE

Scientists and practitioners alike understand that the quality of the scientific evidence behind a commonly accepted view or a generalized clinical practice may vary considerably. The evidence is at times very strong but can be rather tenuous in other situations. The "gold standard," i.e., the highest level of evidence, is thought to be when a solid body of data from several randomized controlled trials (RCTs) is available. Even though it would be desirable to make recommendations based only on such a high standard level of evidence, such data are not always available. Moreover, there are situations in which RCTs cannot even be contemplated. In such cases, one has to rely on other lines of evidence and on the degree of concordance or discordance among a variety of study designs. Controlled but not randomized studies, small experimental research focusing on mechanisms, prospective observational studies, cross-sectional observational research, animal model observations, case studies, surveys of expert views, etc., are typically used to substitute or complement the evidence from RCTs. For the Dose-Response Symposium, we have elected to use a system to qualify the level of evidence that was recently developed at the National Institute of Health (see below). The topic is further addressed in the paper of David Schriger published in this Supplement.

At the initiative of the National Heart, Lung, and Blood Institute (NHLBI), a group of experts from many disciplines developed evidence-based guidelines for the prevention and treatment of obesity and its comorbidities that were published in 1998 (16). The experts invited to the Dose-Response Symposium were instructed to use the four evidence categories as defined in the NHLBI report to assess the level and quality of evidence for each particular issue they were addressing and in developing a series of summary statements.

Table 1 highlights the evidence categories from the NHLBI report. *Evidence Category A* is attained when there is a rich body of data from RCTs. The evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings. Category A therefore requires a substantial number of studies involving a substantial number of participants.

Evidence Category B is reached when there is a limited body of data from RCTs. It is applicable if few randomized trials exist, they are small in size, trial results are somewhat inconsistent, or trials were undertaken in populations that differ from the target population. Category B may also be attained based on the results of meta-analysis of RCTs.

Evidence Category C is granted when the data supporting the conclusion are from uncontrolled or nonrandomized trials, or from cross-sectional or prospective observational studies.

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TABLE 1. The evidence categories with the sources of evidence.

Evidence Category	Sources of Evidence
A	Randomized controlled trial (rich body of data)
B	Randomized controlled trials (limited body of data)
C	Nonrandomized trials (observational studies)
D	Committee consensus judgment

NHLBI. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. The evidence report (16).

Finally, *Evidence Category D* can be given when the provision of some guidance is deemed valuable but there is no compelling scientific or clinical data to justify the use of categories A to C. Category D results from the expert judgment of participants and panel members.

DOSE-RESPONSE: EVOLUTION OF CONCEPTS

The quantification of the amount of physical activity has been the focus of many studies in the past century. Early on the research emphasis was on the measurement and quantification of the energy costs and physiological demands of occupational tasks, personal chores, sports, and leisure-time physical activities. Subsequently, the focus shifted on the conditions under which regular exercise leads to improvement in physical fitness or optimization of physical performance. More recently, we have seen a growing interest for the assessment of physical activity level and measurement of energy expenditure in free-living individuals under a variety of circumstances. At present, a key question is how much physical activity is needed to experience health benefits and avoid premature death. The Hockley Valley Resort 2000 Symposium was designed to review and qualify the evidence bearing on the latter question.

Scandinavian and German physiologists and physicians were the first to investigate the topic of the amount of training necessary to improve fitness and performance. One of the dominant research themes in the 1960s was the differential effects of intermittent and continuous exercise or exercise training (4,9,15,21,22). Another major issue was the difference in cardiovascular and metabolic adaptation to physical work performed at various intensities and durations with the goal of defining the threshold above which performance time was considerably diminished, the so-called "Ausdauerleistungsgrenze" (14). Over the years, various definitions of the concept of "intensity threshold" were proposed but were generally applied more to training and performance issues than to health-related fitness and health outcomes. During the same period, the issue of the minimal amount of regular exercise needed to generate significant health benefits with an emphasis on cardiovascular fitness began to be investigated (5).

How much physical activity with comprehensive experimental manipulations of intensity, frequency, and duration of sessions was first asked in the context of training-induced changes in $\dot{V}O_{2max}$ by Shephard in 1968 (23) (predicted $\dot{V}O_{2max}$) and Davies and Knibbs in 1971 (10) (measured $\dot{V}O_{2max}$). Later, Nördesjo (18) in 1974 investigated the issue in terms of short (6 min) and long (90 min) maximal performance tests. Subsequently, the attention shifted to the conditions under which submaximal working capacity (PWC at a heart rate of 170) could be improved (6). These studies were complemented by a large number of experiments in which one, or at times two, of the three dimensions of intensity, frequency, and duration of sessions were experimentally altered to assess their effects on an outcome that was generally $\dot{V}O_{2max}$. These studies up to 1972 were reviewed by Pollock (20).

An important landmark in the history of the evolution of concepts on the dose-response relationships was the publication in 1978 by ACSM of the Position Statement on the Recommended Quantity and Quality of Exercise for Developing and Maintaining Fitness in Healthy Adults (1). The recommendations can be summarized as follows: intensity of 60 to 90% of maximum heart rate reserve, frequency of 3–5 $d \cdot wk^{-1}$, and duration of 15–60 min per session. Locomotor activities and other activities requiring the involvement of large muscle masses were recommended. In 1990, the Position Statement was revised (2). Although it remained essentially unchanged for the intensity, frequency, and duration recommendations, the document recognized that these exercise recommendations were designed to improve physical fitness and cardiorespiratory endurance rather than health-related fitness. It also emphasized that health benefits could be obtained from engaging in regular exercise performed under conditions that differed from those described in the ACSM Position Statement.

This was followed by a series of very influential reports and pronouncements on the nature of the relationship between regular physical activity and health outcomes and public health messages. A group of about 20 experts met in 1994 at the invitation of the Centers for Disease Control and Prevention and the ACSM to review the evidence and develop a concise public health message. The results of these deliberations were summarized in *JAMA* in 1995 (19). The recommendation was that "every U.S. adult should accumulate 30 min or more of moderate-intensity physical activity on most, preferably all, days of the week." A year later, the very influential report of the Surgeon General of the United States on Physical Activity and Health was published (24). The same recommendation was made with the addition that it applied to people of all ages. The same public health message was adopted by the 13-member panel of the NIH Consensus Development Conference on Physical Activity and Cardiovascular Health (17). An underlying assumption made at all these gatherings of experts and behind the resulting public health message is that the relation between physical activity and health outcomes, particularly mortality rates, is not linear. The common view is that most of the benefits of a regularly active lifestyle can be obtained at low to moderate volumes of physical activity and at less than vigorous intensity (12). In 1998, ACSM published a third Position Statement on the Recommended Quantity and Quality of Exercise for Developing and Maintaining Fitness in Healthy Adults (3). In general, the recommendations were for a larger volume of activity performed at higher intensities than in the public health messages. Finally, *Canada's Physical Activity Guide* was published in 1998 (13). The *Guide* recommended that adults should accumulate 60 min of physical activity every

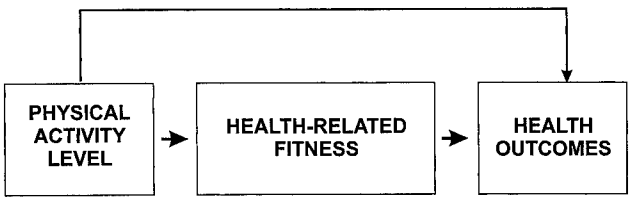


FIGURE 1—The basic paradigm defining the paths from physical activity levels to health outcomes.

day. In this case, the assumption was that most people interpret the public health message in terms of predominantly light intensity activities, thus the necessity to recommend a larger daily volume.

KEY ISSUES CONSIDERED IN THE CONSENSUS PROCESS

The emphasis of the Symposium was on level of physical activity and health outcomes. Figure 1 depicts the basic paradigm underlying the consensus effort. Two paths link physical activity to health outcomes. The first is a direct path in which variation in physical activity level is thought to have an impact on health. The second path is one in which variation in physical activity level translates into changes in health-related fitness, which in turn influence health outcomes. Obviously, references were often made to fitness in the discussion but no systematic attempt was undertaken to arrive at a consensus on the relationships between physical or health-related fitness levels and health outcomes.

The Consensus Committee was faced with the challenge of defining the nature of the relationships between regular physical activity and a whole series of health outcomes ranging from premature mortality to quality-of-life indicators. Even though these relationships can be described in detail by a complex family of curves (11), the problem can also be approached in terms of the three curves shown in Figure 2. The first pattern (curve B) is a linear relationship. This curve seems the most appropriate for the relationship between physical activity level and mortality rates as will be evident from the research summarized in this Supplement. The other two curves (A and C) also provide good fits with specific health outcomes. Curve A best describes the dose-response pattern upon which the current physical activity recommendations are based. It specifies that most of the benefits are attained at low to moderate levels of physical activity. One of the aims of the Consensus Symposium was to examine critically the evidence commonly cited in support of this dose-response pattern. In contrast, curve C specifies that the greatest benefits are obtained only when the level of physical activity is rather high. Some of the health outcomes conform to this curve.

A large number of questions are addressed in the papers prepared by the invited experts and were discussed with the Consensus Committee during the Symposium. The definitions of physical activity, exercise, and fitness were considered, as were frequency and duration of sessions. The topic of fractionation into various physical activity periods was addressed. A considerable amount of time was devoted to the topic of absolute and relative intensity, the issue of thresholds, and the monitoring of intensity. Total amount or volume of physical activity, its quantification, and monitoring also received considerable attention. The benefits resulting from an acute exposure to physical activity versus those expected with regular participation were discussed. The levels of risks versus the anticipated benefits were taken into consideration for a variety of outcomes. Whether the apparent benefits associated with a physically active lifestyle could be imputed to physical activity or energy expenditure *per se* or to ensuing loss of adiposity was a topic that generated much interest. The participants also discussed whether there were any differences in the dose-response relationships between men and women, young versus older people or ethnic groups.

In summary, the goal of the Consensus Symposium was to critically examine the evidence for the dose-response relationships between physical activity levels and health benefits and to identify key issues for future research. The key questions were: Is there a dose-response relation? Does it vary by outcome? What is the exact nature of the relationship? Is there evidence for a threshold? These central questions provided the impetus for an evidence-based Symposium.

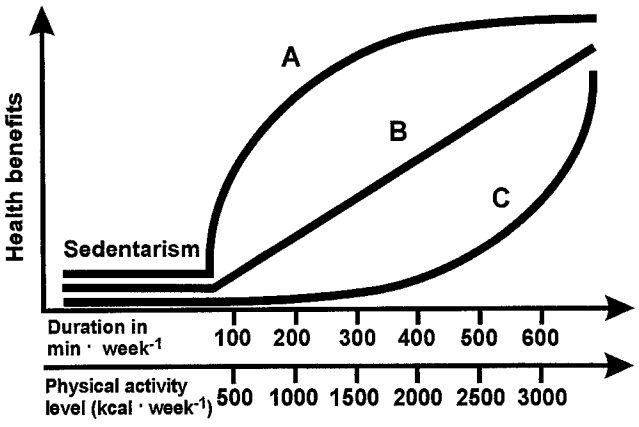


FIGURE 2—Schematic illustration depicting the relationships between physical activity level defined in minutes of participation per week or energy expended. See text for explanation.

CONTENT OF THE SUPPLEMENT

The various texts published in this Supplement of *Medicine and Science in Sports and Exercise* deal with these major questions. After this introduction, the Consensus Statement is presented. This is followed by the papers that focused on definitions and general issues. After a series of related topics (the equivalent of half a day of meeting time), a summary of the evidence as defined by the colleague who chaired the session is presented. Thus, the Supplement includes the Preface, Introduction, Consensus Statement, 24 papers, and 6 summaries from chairpersons. Eleven of these papers deal with specific health outcomes.

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Dose-response issues concerning physical activity and health: an evidence-based symposium

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Regular physical activity is widely accepted as a behavior to reduce all-cause mortality rates and to improve a number of health outcomes. On October 11–15, 2000, Health Canada and the United States Centers for Disease Control and Prevention sponsored a scientific symposium to determine whether there is a dose-response relationship between physical activity and several health-related outcomes and to identify areas for future research. The invited experts reviewed and evaluated the existing literature according to an evidence-based methodology used previously by the National Institutes of Health (5) (Table 1). The Consensus Committee (Panel), consisting of individuals with experience and knowledge in health areas of concern from outside the field of exercise science, reviewed and evaluated the evidence presented, assigned it to an evidence category, and identified topics for future research. The manuscripts upon which the consensus was based and the report of the Consensus Committee are published concurrently in this issue of *Medicine & Science in Sports & Exercise*.

Most of the evidence currently available seems to be related to the effects (benefits or risks) of regular physical activity rather than to the relationship between dose and response. Therefore, the Panel decided to summarize the evidence for the effects of participation in regular physical activity, because the Panel found this useful and necessary to properly understand the dose-response data.

The key terms used during the Symposium and in this report are described in detail by Howley (4). Briefly, health is defined as a human condition with physical, social, and psychological dimensions. Physical activity is defined as any bodily movement produced by contraction of skeletal muscle that substantially increases energy expenditure. The dose of physical activity, or exercise, needed to bring about a particular health benefit response is described by the characteristics of frequency, duration, intensity, and type of activity. Frequency is described as the number of activity sessions per time period (e.g., day or week). Duration refers to the number of minutes of activity in each session. Intensity describes, in relative or absolute terms, the measured or estimated effort (energy cost) associated with the physical activity. Physical activity may be of a leisure time or occupational type activity. Physical fitness is defined as a set of attributes (i.e., cardiorespiratory endurance, skeletal muscle endurance, skeletal muscle strength, etc.) that relate to the ability to perform physical activity. The product of frequency, duration, and intensity yields the total energy expenditure associated with the physical activity and is a measure of the volume of exercise. The gross cost of an activity is the total energy expenditure, which includes resting metabolic rate and the cost of the activity itself. The net cost is that associated with the activity alone.

BACKGROUND

Concepts and Methods

Appropriate measurements of physical activity are needed to judge whether there is a dose-response relationship between physical activity and health. Ideally, the important components of physical activity include measurements of frequency and duration (time) and intensity (absolute and relative). With these measurements, it is possible to calculate the dose (or volume) of exercise. Unfortunately, many studies have not collected detailed measures on intensity, duration, and frequency but have used subjective assessments such as "little, moderate, and heavy." The dose equals the energy expended in physical activity and is one of the potential mediators of the health benefits of physical activity. Therefore, relatively accurate measurements of both the time spent in physical activity and intensity of physical activity are needed. This is a problem because the methods used in field studies (questionnaires, physical activity records, and recall diaries) are imprecise, particularly for estimating low levels of physical activity. These methods rely on self-reports of the individual's perceived intensity of physical activity. They may not reflect the absolute intensity across all age and sex groups required for converting the perceived levels of exercise intensity into METs, a commonly used unit used to estimate the metabolic cost (oxygen consumption) of physical activity. One MET

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Proceedings for this symposium held October 11–15, 2000, Ontario, Canada.

TABLE 1. Categories of evidence.[a]

Category A: Evidence is from endpoints of well-designed RCT (or trials that depart only minimally from randomization) that provide a consistent pattern of findings in the population for which the recommendation is made. Category A, therefore, requires substantial numbers of studies involving substantial number of participants.
Category B: Evidence is from endpoints of intervention studies that include only a limited number of RCT, post hoc or subgroup analysis of RCT, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, and the trial results are somewhat inconsistent, or the trials were undertaken in a population that differs from the target population of the recommendation.
Category C: Evidence is from outcomes of uncontrolled or nonrandomized trials or from observation studies.
Category D: Expert judgment is based on the panel's synthesis of evidence from experimental research described in the literature and/or derived from the consensus of panel members based on clinical experience or knowledge that does not meet the above-listed criteria. This category is used only in cases where the provision of some guidance was deemed valuable but an adequately compelling clinical literature addressing the subject of the recommendation was deemed insufficient to justify placement in one of the other categories (A through C)

[a] From reference 5.

equals the resting metabolic rate (~kcal·min^{-1} or 3–5 mL O_2·kg^{-1}·min^{-1}).

The lack of a gold standard for the precise quantification of the energy expenditure of physical activity has hampered the development of universally acceptable and accurate field assessment techniques. A variety of direct and indirect methods are presently used to assess physical activity. Portable oxygen uptake devices and improved sensors of bodily movements and temperature continue to be investigated, but more work and better consensus regarding their uniform application are needed.

Older and/or obese individuals are likely to perceive a given absolute level of physical activity as more intense than younger, fit, less obese individuals. To convert perceived levels of physical activity intensity into meaningful absolute intensity levels (and therefore into energy expenditure of physical activity), it is helpful to have conversion factors. The Panel recommends that the conversion factors provided in Table 2 be widely used by investigators to calculate indices of volume, as well as the absolute and relative levels of physical activity. This table allows the data reported in relative intensity to be converted into absolute intensity.

It is important to consider the intensity of physical activity as part of the dose-response relationship because of its known effect on fitness. Fitness, commonly assessed in terms of peak workload or maximal oxygen uptake ($\dot{V}O_{2max}$), is improved more by high- than low-intensity physical activity. If fitness is an intermediate factor between physical activity and health benefits, then measurement of the intensity of physical activity may be important in assessing dose response. $\dot{V}O_{2max}$ has been used as a measure of the "dose" of physical activity. Given the significant constitutional, interindividual variability in $\dot{V}O_{2max}$, this may not be ideal. The measurement of fitness itself, however, is more accurate than current field measurements of physical activity. There is some evidence that fitness could be more strongly related to some health outcomes than physical activity. These observations, however, may be due in part to the greater accuracy in the measurements of fitness. Other measurements of fitness include the assessments of submaximal exercise endurance and the heart rate response to a given workload.

Two further issues need to be considered when testing for a dose-response relationship between physical activity and health outcomes. The first relates to the increased risk to adverse health outcomes as the volume and intensity of exercise are increased. In this case, the net benefit of higher levels of physical activity may not be as great as predicted (Fig. 1). The second issue relates to the likelihood that the overall physical activity level (both activities of daily living and occupational physical activity) of populations is decreasing. Consequently, estimating the volume of physical activity needed to reduce health risks from data generated by older studies could be problematic.

Although the resistance training and flexibility issues are important to global health outcomes, the Symposium focused mainly on physical activity with an emphasis on aerobic activities.

Fractionalization of Physical Activity

Fractionalization of physical activity can be understood as: 1) comparing one continuous session of exercise with several short sessions of the same total duration; or 2)

TABLE 2. Classification of physical activity intensity.

	Endurance-Type Activity									
	Relative Intensity			Intensity (METs and %$\dot{V}O_{2max}$) in Healthy Adults Differing in $\dot{V}O_{2max}$						
				$\dot{V}O_{2max}$ = 12 METs		$\dot{V}O_{2max}$ = 10 METs		$\dot{V}O_{2max}$ = 8 METs		$\dot{V}O_{2max}$ = 5 METs	
Intensity	%$\dot{V}O_2$R[a]/%HRR	%HR_{max}[b]	RPE[c]	METs	%$\dot{V}O_{2max}$[d]	METs	%$\dot{V}O_{2max}$	METs	%$\dot{V}O_{2max}$	METs	%$\dot{V}O_{2max}$
Very light	<20	<50	<10	<3.2	<27	<2.8	<28	<2.4	<30	<1.8	<36
Light	20–39	50–63	10–11	3.2–5.3	27–44	2.8–4.5	28–45	2.4–3.7	30–47	1.8–2.5	36–51
Moderate	40–59	64–76	12–13	5.4–7.5	45–62	4.6–6.3	46–63	3.8–5.1	48–64	2.6–3.3	52–67
Hard	60–84	77–93	14–16	7.6–10.2	63–85	6.4–8.6	64–86	5.2–6.9	65–86	3.4–4.3	68–87
Very Hard	≥85	≥94	17–19	≥10.3	≥86	≥8.7	≥87	≥7.0	≥87	≥4.4	≥88
Maximal	100	100	20	12	100	10	100	8	100	5	100

Modified from Table 1 of ACSM Position Stand (ref. 5).
[a] %$\dot{V}O_2$R - percent of oxygen uptake reserve; %HRR - percent of heart rate reserve.
[b] %HR_{max} = 0.7305 (%$\dot{V}O_{2max}$) + 29.95 (reference #20); values based on 10-MET group.
[c] Borg Rating of Perceived Exertion 6–20 scale (reference #8).
[d]%$\dot{V}O_{2max}$ = [(100% − %$\dot{V}O_2$R) MET_{max}^{-1}] + %$\dot{V}O_2$R; personal communication.
(From ref. 4).

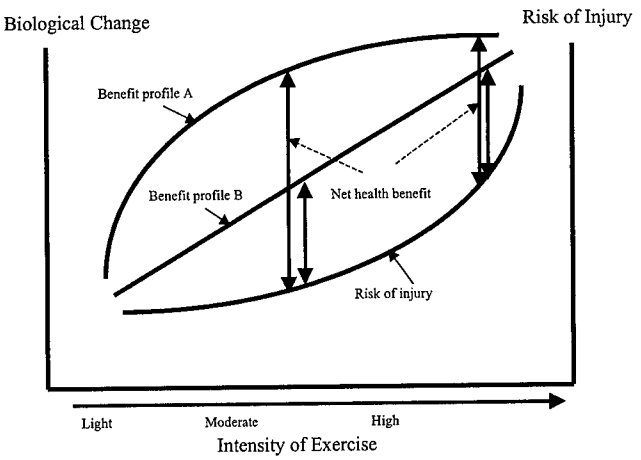


FIGURE 1—The relationship of exercise intensity to biological change (for two dose-response profiles) and risk injury. Net health benefit for moderate- and high-intensity exercise displayed; from ref. 3.

comparing a session of moderate-to-hard exercise with a session of longer duration, lower intensity, but equivalent energy expenditure, i.e., "trading intensity for duration." In randomized short-term studies, which compare the training effects of one long exercise session per day to several short ($\geq$10 min) exercise sessions per day at the *same* intensity, two short sessions appear generally as effective as a single session of the same total duration. Moreover, improvements in $\dot{V}O_{2max}$ are found equal for both programs in randomized long-term training studies (Category B).

When considering the issue of "trading intensity for duration," short-term studies suggest that heavy exercise is more likely to induce negative energy balance than light exercise (Category C). In long-term studies, there is evidence that high-intensity training elicits a greater increase in $\dot{V}O_{2max}$ than low-intensity training for the same total energy expenditure (Category B).

Acute and Chronic Effects of Physical Activity

Acute effects of physical activity refer to health-related changes that occur during and in the hours after physical activity, which are not further improved with additional physical activity. Chronic effects associated with physical activity occur over time due to changes in the structure or function of various body systems, independent of acute effects. However, the acute exercise response and the chronic adaptations to exercise training cannot be viewed in isolation because frequent repetition of isolated sessions with transient responses produces more permanent adaptations (i.e., chronic effect). Therefore, there may be an interaction between the acute and chronic effects of physical activity. In some instances, exercise may have an acute effect that disappears rapidly with no influence on the response to subsequent exercise. This acute exercise, if repeated, could also have a cumulative effect or one that diminishes gradually. The effects of repeated, acute, low-intensity, physical activities may also result in small changes that may not be detectable in clinical studies but still have a discernible effect if adopted by large populations. When evaluating the acute effects of exercise, the timing of health assessments must be taken into account because of circadian variation in outcomes and changes in plasma volume due to the exercise.

There is an extensive literature on the acute effects of physical activity on atherosclerotic cardiovascular risk factors. There are 12 controlled studies in small numbers of subjects that show a single session of exercise, at an intensity of 50–80% $\dot{V}O_{2max}$, results in the lowering of serum triglycerides (3–15%) and an increase in serum high-density lipoprotein (HDL)-cholesterol (4–43%). These effects can be observed 18–24 h after an exercise bout and can persist for up to 72 h. A single session of prolonged heavy exercise (e.g., a marathon run) is also followed by a decrease in low-density lipoprotein (LDL)-cholesterol (4–38%), which in part is due to an acute expansion of plasma volume. The Panel considers the evidence for the acute changes in serum triglycerides and HDL-cholesterol with exercise to be strong (Category A). The evidence for the acute reduction in LDL-cholesterol with exercise is also considered strong (Category A) but may not have physiological relevance. The Panel finds no evidence for a dose-response effect of acute exercise on the lipoprotein changes.

A single session of exercise at an intensity of 50–100% of $\dot{V}O_{2max}$ produces a lowering of 18–20 mm Hg in systolic and 7–9 mm Hg in diastolic blood pressure. These changes remain for 12–16 h after the exercise. The maximal changes in blood pressure have been observed in individuals with mild (Stage I) hypertension. The Panel considers the evidence for the blood pressure lowering by acute exercise to be strong (Category A). However, there is insufficient evidence to define a dose-response effect.

The effects of acute exercise on blood glucose and insulin sensitivity at the intensity of 55–75% $\dot{V}O_{2max}$ have been studied in seven controlled trials with a small number of subjects with type 2 diabetes mellitus. The data indicate a lowering of 20–40 $mg \cdot dL^{-1}$ (1–2 $mmol \cdot L^{-1}$) of blood glucose for 2–3 d (Category A). There is insufficient evidence to define any dose-response effect of acute exercise on glucose metabolism.

In summary, acute exercise has beneficial effects on lipoproteins, blood pressure, and insulin sensitivity. However, there is presently insufficient evidence to define a dose-response effect.

Individual Variability

The HERITAGE Family study has demonstrated a considerable between subject variability in fitness and risk factor responses to a given amount of physical activity (1). These responses aggregate within families (Category B) emphasizing the considerable heterogeneity that may be anticipated when measuring a dose-response to physical activity. Such heterogeneity should be taken into account when analyzing results from both observational and interventional studies and when considering power calculations for future investigations. This familial heterogeneity underscores the importance of understanding the influence of

specific genotypes as confounders in the relationship between physical activity and health benefits.

DOSE-RESPONSE IN PHYSICAL ACTIVITY AND HEALTH OUTCOMES

All-Cause Mortality

The hypothesis that physical activity and physical fitness promote health and longevity has been recognized for centuries. What is less clear is the shape of the dose-response curve between physical activity and all-cause mortality rates. This is of particular interest because of the current change in recommendation for 30-min moderate-intensity physical activity on most days of the week in the place of the previous recommendation that advocated vigorous-intensity exercise for 20 min continuously three times weekly. With the high prevalence of sedentary behavior in modern industrialized societies, it is important to ascertain the minimum dose of physical activity required to decrease all-cause mortality rates. A search of the literature over the past 34 years that addressed all cause-mortality rates (excluding papers that examined only two levels of physical activity or were not written in English) identified 44 papers. Of these, five assessed physical fitness and one both physical activity and fitness. Of the remaining 38 papers, most assessed leisure-time, three assessed occupational, and nine both types of physical activity. Of importance, all assessed the relationship between the volume of physical activity and all-cause mortality rates. Most of these demonstrated a dose-response relationship between physical activity and all-cause mortality rates. Five noted a threshold effect, whereas five found no significant association between physical activity and all-cause mortality. Of the 17 studies that tested for a linear trend of declining all-cause mortality rates with increasing volume of physical activity, most found a significant inverse linear trend in at least one population subgroup. It was not possible to assess the impact of the components of exercise volume (intensity and duration) or frequency in these studies, apart from their contribution to the volume of the physical activity.

The Panel concludes that there is Category C evidence for a dose-response relationship between the volume of physical activity and all-cause mortality rates in adult men and women of all ages from the United States and Europe. The slope of this inverse relationship between physical activity and all-cause mortality is not clearly defined, but in most of the studies the relationship appears to be linear. The minimal effective dose is not well defined, but physical activity expending 1000 kcal·wk^{-1} (4200 kJ·wk^{-1}) is associated with as much as a 30% reduction in all-cause mortality rates. There is a suggestion that volumes of physical activity as low as 500 kcal·wk^{-1} might demonstrate a slight favorable effect on all-cause mortality, but this requires further study.

Cardiovascular Disease

Cardiovascular disease (CVD) contributes substantially to morbidity and mortality throughout the world. There have been no randomized-controlled trials conducted to determine the effect of physical activity or fitness on CVD; however, a large body of prospective observational evidence is available.

Overall, there is a consistent inverse dose-response relationship between physical activity and both the incidence and mortality rates from all cardiovascular and coronary heart disease (Category C). This relationship, which derives from earlier studies that assessed occupational physical activity as well as later ones using leisure-time physical activity, is evident when either the volume or intensity of physical activity are used for assessment. The majority of studies have been conducted in men. However, from the more limited data available, the relationship appears to be similar in women. The shape of the dose-response curve appears to be linear when response is measured in terms of relative risk.

The prospective observational studies that have examined the dose-response relationship between physical activity and the incidence and mortality rates from stroke, however, do not provide consistent evidence of a dose-response relationship. Several studies report a "U"-shaped relationship, with higher disease rates among those with the lowest and highest levels of physical activity. Most studies have not reported the rates of hemorrhagic stroke separately from those of ischemic stroke, which may be relevant given the different pathogenesis of the two conditions.

In summary, the Panel finds an inverse and linear dose-response relationship between physical activity and both the incidence and mortality rates from all cardiovascular and coronary heart disease (Category C).

Blood Pressure and Hypertension

A meta-analysis of 44 RCT (involving 68 study groups and 2677 subjects, both men and women aged from 21 to 79 yr) shows that aerobic training, at an intensity between 30 and 85% of maximal exercise performance (determined by heterogenous methods) reduces systolic/diastolic blood pressure significantly ($-2.6/-1.8$ mm Hg in normotensive and $-7.7/-5.8$ mm Hg in hypertensive groups). Thirty-five RCT comprising 45 study groups applied only one training intensity that ranged from 50 to 85% of maximal exercise performance. Weighted meta-regression analysis shows that net change in systolic and diastolic blood pressure is not significantly related to the training intensity nor time per session. The duration of the training program is, however, a significant determinant of the response of the systolic, but not of diastolic, blood pressure. A review of the nine RCT that address dose-response issues reveals that training, at about 50% of maximal exercise tolerance, is as effective in reducing blood pressure as training at about 75%. These studies involved a smaller number of subjects.

In summary, the Panel considers the RCT evidence to be strong for training at ~ 50% of maximal exercise tolerance to be effective in reducing blood pressure (Category A). Training at high-intensity level does not appear to provide additional benefit (Category B).

Blood Lipids and Lipoproteins

Fifty-one studies (28 RCT), with a duration of exercise of more than 12 wk involving about 4700 subjects aged 18–80 yr (60% men), are available for review. Ten focus on subjects with normal body weight (BMI < 25), 25 studies on overweight subjects (BMI 25–29.9), and 14 studies on obese individuals (BMI ≥ 30). In some studies, the intervention includes both physical activity and dietary change. Only eight studies were performed in subjects with hypercholesterolemia and/or hypertriglyceridemia. The physical activity program used in the studies was aerobic, 50–80% $\dot{V}O_{2max}$ or % heart rate reserve (HRR), three to five times per week for 30–60 min, with an estimated energy expenditure of 500–5000 kcal·wk^{-1}. On average, training resulted in 16% improvement in $\dot{V}O_{2max}$ (range from < 3% to > 50%).

The most common lipid change (in 40% of studies) is an average increase of 4.6% in HDL-cholesterol in both men and women of all ages. Reduction in LDL-cholesterol (−3.7%), triglycerides (−5%), and total cholesterol (−1%, nonsignificant) are observed less consistently than the increase in HDL-cholesterol. The Panel considers there is substantial evidence that moderate to hard exercise has a favorable influence on the blood lipid and lipoprotein levels (Category B). A few studies show that the activity-induced increase in HDL-cholesterol involves primarily HDL-2-cholesterol and that the mechanism for this effect is increased lipoprotein lipase activity (Category B). A part of the effect induced by regular physical activity may be related to a change in body and fat mass (Category B). Age and sex do not seem to be predictors of responsiveness of HDL-cholesterol to physical activity (Category B). Baseline lipid levels appear to strongly influence the lipid response in that a lower pretraining HDL-cholesterol is associated with a greater HDL-cholesterol response, although the pattern is not observed in all studies .

In summary, there are few studies that have evaluated the dose-response effects of different exercise intensities on blood lipids and they provide conflicting evidence.

Coagulation and Hemostatic Factors

Although acute exercise and physical activity have long been recognized to alter blood coagulation, there have been no controlled or uncontrolled studies of a dose-response relationship on overall measures of coagulation. However, platelet function and fibrinolytic factors have been investigated in this context. This topic has received much attention since activation of the hemostatic system has been implicated as a mechanism for sudden cardiac death after acute exercise. The effects of regular physical activity on several aspects of blood coagulation have been investigated in RCT. The best-studied effect is that of physical activity on platelet adhesion. Newer techniques that take advantage of monoclonal antibodies against platelet surface receptors have demonstrated that strenuous exercise activates platelets in sedentary, and to a lesser extent, in physically active individuals. Regular physical activity decreases platelet adhesiveness and aggregation at rest and during acute strenuous exercise (Category B). None of these data, however, allow for an assessment of a dose-response relationship.

Fibrinogen has been identified as an independent risk factor for cardiovascular disease and mortality. An inverse relationship between fibrinogen concentrations and physical activity level is consistently reported in cross-sectional studies. However, in RCT, the results have been discrepant, and no studies have tested for a dose-response relationship.

The measurable fibrinolytic factors such as tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI-1) have been assessed in a limited number of primarily cross-sectional studies because exercise also acutely alters fibrinolysis. Acute exercise increases t-PA, but only strenuous activity decreases PAI-1 (Category B). However, their levels are generally unchanged by regular physical activity (Category C). Specific genotypes of PAI-1 and fibrinogen could explain some of the variability commonly observed in response to acute physical activity.

In summary, the Panel finds no evidence for a dose-response relationship between physical activity and coagulation and hemostatic factors.

Overweight, Obesity, and Fat Distribution

The impact of physical activity in the prevention and treatment of obesity and its comorbidities has been reviewed using identical methodology (2). There is evidence of a linear dose-response relationship between the volume of physical activity and the amount of weight loss in studies of ≤ 16-wk duration when diet is controlled (Category A). The amount of body weight or fat loss found in RCT is consistent with the excess energy expended. The published studies thus far relate primarily to Caucasian populations, and the preponderance of studies are in men. However, trials lasting 24 wk or more do not show a dose-response effect. There is insufficient evidence to conclude that a dose-response relationship exists between physical activity and abdominal fat loss independent of weight loss. There is evidence to show that visceral fat loss is comparable between groups who lose weight via dieting and those who lose weight by the negative energy balance produced by physical activity (Category B). The Panel finds that increased levels of physical activity are associated with the prevention of weight gain over time, but the nature of the dose-response relationship is not clear (Category C). The Panel notes that there is evidence for other health benefits as a result of a modest weight loss associated with physical activity.

Type 2 Diabetes Mellitus

A number of relatively large clinical trials have been performed to evaluate the effect of physical activity on glucose homeostasis in patients with type 2 diabetes mellitus. A positive effect has been found in most, but not all, of these trials. The magnitude of the improvement in blood glucose control attributable to exercise intervention is generally modest but clinically important (a decrease in %HbA1c of 0.5–1%). It is difficult to dissociate the effect of exercise from those of dietary intervention and adjustment

in medication in most of the reported studies. The Panel agrees that regular physical activity may modestly improve blood glucose control in patients with type 2 diabetes (Category B) but finds no evidence for a dose-response relationship.

There is strong epidemiological evidence that regular physical activity reduces the incidence of type 2 diabetes mellitus (Category C). Large prospective studies, performed in men and in women, have shown that type 2 diabetes mellitus develops less frequently in the individuals who exercise regularly. In the Harvard Alumni Study, a 6% linear decrease in the age-adjusted risk for the development of diabetes has been found for each 500 kcal expended by physical activity in weekly leisure time. Similar findings are reported by a Swedish study of middle-aged men and by a recent study in African-Americans. Furthermore, four large epidemiological studies in both men and women suggest that vigorous regular physical activity protects against the development of type 2 diabetes. The Panel considers the evidence strong but of Category C. One recent study reported a strong dose-response gradient across fitness categories with a three-fold higher risk of developing type 2 diabetes in "low-fit" men compared to "high-fit" men. Further randomized and nonrandomized studies suggest that exercise, and exercise combined with dietary intervention, retard the transition from impaired glucose tolerance to type 2 diabetes (Category C).

In men with confirmed diabetes, physical activity and moderate-to-high levels of cardiorespiratory fitness appear to reduce the risk of CVD and all-cause mortality (Category C). There is a steep inverse dose-response gradient of mortality risk across categories of fitness (Category C). These results are observed after adjustment for multiple other risk factors.

In summary, the Panel finds Category C evidence for a dose-response relationship between physical activity and the prevention of type 2 diabetes and physical activity and CVD and all-cause mortality in type 2 diabetics.

Cancer

A large number of observational studies have suggested that physically active populations have lower overall cancer incidence and mortality rates. However, confounding factors (differences in diet and other health behaviors) make interpretation of these studies difficult. The strongest evidence for a beneficial effect of physical activity is for colon cancer (Category C). Thirty-five of 49 studies show an association of increased physical activity with reduced incidence rates. Although 20 studies are interpreted as showing a dose-response relationship, most of these compared only two levels of physical activity. Therefore, the Panel considers there is only moderate evidence for a dose-response effect (Category C). It is not possible to determine the shape of any dose-response because of the lack of data on the volume of physical activity. There is conflicting evidence that increased physical activity is associated with a lower risk of other types of cancer.

In summary, the Panel finds Category C evidence for a dose-response relationship between physical activity and risk for colon cancer.

Low Back Pain, Osteoarthritis, and Osteoporosis

Low back pain, osteoarthritis, and osteoporosis are major causes of societal disability. Physical activity, in particular leisure-time physical activity, has the potential to both worsen and prevent the development of these conditions. Additionally, supervised physical activity could prevent the worsening of symptoms.

For low back pain, the evidence for a beneficial effect of physical activity is conflicting. Two RCTs suggest that leisure time physical activity may have a primary preventive effect, whereas prolonged occupational and sports activities increase the risk (Category B). For secondary prevention, there is no evidence that specific exercises are beneficial although exercise is useful within an active rehabilitation program (Category C).

For osteoarthritis, there is no evidence for a preventive effect of physical activity in weight-bearing joints although there is evidence for increased risk of osteoarthritis from heavy physical activity from sports or certain occupations (Category C). Supervised exercise may, however, be effective in the treatment and rehabilitation of patients with osteoarthritis of the knee (Category B).

For osteoporosis, peak bone mass is achieved in youth, and the subsequent rate of bone loss is considered important in determining bone mass at the age of 70 yr. Both cross-sectional and longitudinal studies and two RCT indicate that physical activity in young adults can contribute to increased peak bone mass (Category B). However, no information is available about the dose-response relationship. Quantitative analysis provides strong evidence that physical activity is effective in maintaining bone mass in premenopausal women and in decreasing subsequent bone loss after the menopause (Category A). No data regarding the dose-response relationship is available, but it appears that the effect is related to high-intensity activities. Intensive training for prolonged periods, such as seen in competitive women runners and in subjects with low body weight and eating disorders, may result in osteopenia. Such women are at particular risk for stress fractures.

In summary, physical activity may have both beneficial and detrimental effects on low back pain, osteoarthritis, and osteoporosis. It is not possible to quantify specific health benefits of physical activity in the absence of information about dose responses. Nevertheless, there is considerable potential for a beneficial action in the prevention of osteoporosis.

Quality of Life and Independent Living in the Elderly

The main question is whether regular physical activity contributes to enhanced quality of life in subjects 65 yr and older as reflected by sense of well being, physical and mental function, and independent living. Although

resistance training and other activities are recognized as important, the review focused primarily on physical activity alone. Cross-sectional studies support a relationship between physical activity and overall well being, but evidence from intervention studies is equivocal. Cross-sectional studies indicate a positive influence of regular physical activity on physical function (Category C). In intervention studies, some of which are randomized, this positive relationship is also observed. A greater improvement in activity of daily living appears to be associated with increasing levels of energy expenditure (Category C). Physical activity intervention studies generally show positive results on walking distance but not speed (Category B). There is conflicting evidence on physical activity and mental function. The most consistent evidence is that regular physical activity postpones disability and promotes independent living in the elderly (Category C).

In summary, the Panel finds Category C evidence for a dose-response relationship between physical activity and an improvement in activity of daily living.

Depression and Anxiety

Individuals with higher levels of physical activity are less likely than those with lower levels to develop depressive illness in observational studies (Category C). Aerobic exercise training for 6–12 wk in mild-to-moderate depression and anxiety is consistently associated with an improvement of symptoms of a magnitude comparable to that obtained with some pharmacological agents, although the response may be slower (Category B). Neither the intensity of the exercise nor the level of fitness is clearly associated with the magnitude of the response (Category B). The data are insufficient to assess the importance of exercise frequency and duration, and the merits of resistance compared with aerobic training. The effect of physical activity on general mood and anxiety in the overall population is important but was not addressed in this review.

In summary, the Panel finds no dose-response relationship between physical activity and depression and anxiety.

Age, Sex, and Prior Health Status

Age, sex, and prior health status may influence the dose-response relationship with physical activity. For the purposes of this Symposium, it was not possible to explore their influence on all of the outcome variables discussed, and the analysis was therefore restricted to systolic blood pressure (SBP), diastolic blood pressure (DBP), serum triglycerides, and HDL-cholesterol.

Age has little effect on the response to exercise training for SBP, DBP, triglycerides, and HDL-cholesterol (Category B). For instance, the magnitude of blood pressure decreases in all age groups is in the range of 3–8 mm Hg for SBP and 2–6 mm Hg for DBP. Women appear to have an attenuated response compared with men for SBP and DBP with the reduction being generally 1–3 mm Hg less (Category C). The rise in HDL-cholesterol in response to exercise training is also attenuated in women (Category C), whereas a difference in triglyceride response is equivocal.

Subjects with established hypertension appear to have a more favorable response in blood pressure lowering to exercise training than normotensive subjects (Category B). Similarly, subjects with a previous history of myocardial infarction show somewhat larger falls in triglycerides and increases in HDL-cholesterol compared with those with no known coronary disease. This is likely to be related to the higher pretraining level of triglycerides and lower level of HDL-cholesterol in these subjects (Category B).

In summary, the dose-response relationships to physical activity have not been investigated in the different age, sex, and health status groups.

Population Attributable Risk Percentage of Disease due to Physical Inactivity

The calculation of a population attributable risk percentage (PAR%) provides a useful estimate of the burden of a particular disease or condition attributable to a given exposure—in this case, the percentage of specific mortality or morbidity that is attributable to physical inactivity. Using this approach, it has been estimated that the PAR% of cardiovascular disease mortality due to physical *inactivity* is approximately 35%. This technique can be extended to examine multiple levels of physical activity and to adjust for confounding variables. To do so requires population-specific data on the prevalence of the various levels of physical activity and the relevant confounding variables, as well as the morbidity and mortality rates experienced for each level of physical activity. Such data are not currently available for a representative population sample. The Panel considers this to be an important topic for future research. Both the public and policy makers will find the PAR% method useful for assessing the impact on health outcomes of sedentary life compared with the potential health and economic benefits of a physically active population.

SUMMARY AND CONCLUSIONS

Beneficial Effects of Physical Activity

The Panel concludes that a large body of evidence supports the contention that physical activity produces a number of major health benefits. Regular physical activity is associated with a reduction in all-cause mortality, fatal and nonfatal total cardiovascular disease, and coronary heart disease. It is also associated with a reduction in the incidence of obesity and type 2 diabetes mellitus, and an improvement in the metabolic control of individuals with established type 2 diabetes. Furthermore, physical activity is associated with a reduction in the incidence of colon cancer and osteoporosis. Further benefits of regular physical activity include improved physical function and independent living in the elderly. Individuals with high levels of physical activity are less likely than those with lower levels to develop depressive illness. Moreover in those with mild-to-

moderate depression and anxiety, prescribed physical activity is associated with an improvement in symptoms.

The Panel also recognizes the favorable impact of physical activity on several cardiovascular risk factors, including a reduction in blood pressure, improvement in the plasma lipid profile, and alterations in coagulation and hemostatic factors.

Dose-Response Relationship of Physical Activity to Health Outcomes

There is an inverse and generally linear relationship for the rates of all-cause mortality, total CVD, and coronary heart disease incidence and mortality and for the incidence of type 2 diabetes mellitus. It is more difficult to determine a dose-response relationship for other health outcomes. There are several reasons for this difficulty: 1) the absence of studies defining a dose-response; 2) lack of field methods sensitive and accurate enough to determine the dose of physical activity; 3) small effects of physical activity on some outcomes; 4) uncontrolled confounding factors such as genetic variability; and 5) simultaneous changes in body weight and composition that accompanies physical activity. The Panel suggests that where a dose-response relationship cannot be proven, it may be sufficient to discover a level of physical activity or fitness that results in a beneficial effect.

The greater the intensity and volume of exercise, the greater the risk of injury and harm, especially musculoskeletal for most individuals and cardiovascular for those with underlying disease. When attempting to establish an optimal dose of physical activity for health, intensity is especially relevant because it is the major contributor to exercise-induced medical complications. The Panel suggests that, when assessing dose-response, consideration be given not only to the dose that induces the greatest health benefit but also to the potential risk in a particular population.

Research Recommendations

Although the field of physical activity is rich in high-quality observational data and studies of physiology, there are a limited number of RCT on the quantitative effect or dose relationship of physical activity and health outcomes. If the results of RCT on the benefits of physical activity are to be convincing, they must be based on precise and reproducible methodology. To better evaluate the dose-response relationship, attention needs to be paid to the following:

Study design: 1) development of a gold standard for precise field measurement of physical activity; 2) evaluation of the health effects of multiple levels of physical activity, volume, intensity, and fitness; 3) application of innovative statistical procedures; 4) assessment of potential adverse effects of physical activity; and 5) study populations being representative of all ages, both sexes, ethnic groups, and those with a variety of health states.

Study evaluation: 1) strict adherence to regimens of physical activity in future studies must be promoted and carefully monitored; 2) importance of defining a minimum effective dose of physical activity for health benefit and attention being paid to any additional benefits that accrue from increased levels of activity; and 3) in the design and analysis of future studies, attention to the newly recognized interindividual variability in the response to physical activity and its genetic basis.

Consideration should be given to the development of large, multicenter randomized controlled trials on the effect of multiple levels and patterns of physical activity on a range of health outcomes and risks. The Panel recognizes the challenge that would be presented by such studies but observes that such studies have been done and are underway for other important preventive and therapeutic interventions.

If the full benefits of current and future knowledge about the benefits of physical activity are to be realized, substantial and sustained effort will be needed to ensure the practical application of this knowledge into clinical settings and for entire populations.

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Analyzing the relationship of exercise and health: methods, assumptions, and limitations

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ABSTRACT

SCHRIGER, D. L. Analyzing the relationship of exercise and health: methods, assumptions, and limitations. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S359–S363. The papers in this supplement to *Medicine and Science in Sports and Exercise* seek to summarize our knowledge of the dose-response relationship of exercise with a variety of health outcomes. This type of rigorous evidence summation has become quite popular in the past 10 years as health care providers and policymakers seek to distinguish interventions that are helpful—the expected benefits justify human and economic costs—from those of no or uncertain benefit (7). Proponents of "evidence-based medicine" argue that in contrast to old-style literature reviews in which the writer, typically an "expert," develops a thesis and cites only those publications that support his point of view, an evidence-based approach finds all of the evidence and objectively weighs it to determine the "truth" (20,22). Although such methods offer the promise of increased objectivity, they are not immune to bias, and readers should understand that the declaration that something is "evidence-based" is no guarantee of its veracity. In fact, because the literature virtually never includes studies that perfectly match the setting and personal circumstance of the patient under treatment, "evidence-informed medicine" would be a more honest title for care grounded in systematic reviews of the literature (23). This paper begins with a discussion of potential theoretical problems with systematic reviews and concludes by considering specific problems that members of the panel were likely to encounter when evaluating the literature on exercise and health. These concepts were presented in the initial lecture of the conference so that the 24 lecturers and 6 members of the consensus panel would be forewarned of the dangers that lay ahead. **Key Words:** PHYSICAL FITNESS, EVIDENCE-BASED MEDICINE, BIAS (EPIDEMIOLOGY), DATA INTERPRETATION, STATISTICAL

A HISTORICAL PERSPECTIVE

In 1973, Wennberg and Gittlesohn (27) documented huge variations in health care practices among adjacent regions of northern New England. In 1986, Chassin et al. (3) showed that variations of similar magnitude could be found when comparing large geographic regions. The recognition of large variations in health care delivery at a time when health care costs were burgeoning, provided the impetus for the development of guidelines designed to standardize the delivery of health care. In the early 1990s, Eddy (8,9) stressed the importance of evidence in the development of guidelines and offered methods for systematically using evidence to establish policy. Subsequently, the McMaster University group (20,22) articulated the premises of evidence-based medicine.

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THE ROLE OF SYSTEMATIC REVIEWS

The systematic evaluation of evidence is perhaps best understood as one element in a continuous quality improvement cycle for medical care (Fig. 1). A specific question is developed; the literature is searched; relevant articles are selected, abstracted, and critiqued; results are portrayed in a tabular (the Evidence Table) (8) or graphical format; and qualitative or quantitative (meta-analysis) summation of the articles is performed (Table 1). After the evidence has been summarized, gaps in knowledge can be identified and research questions developed (12). The publication of new research findings completes the cycle and sets the stage for another round of evidence evaluation.

The compiled evidence can be offered to the medical community as is or incorporated into clinical guidelines. Because this panel was instructed to limit its activity to the summation of evidence (the activities within the dotted box in Fig. 1), I will not give further consideration to the guideline development process except to say that interested readers may consult the references (8,10,12,17).

This model has many appealing features. Wouldn't it be wonderful if public health and medical advances were made through such a coherent, organized effort? Unfortunately, there is historical evidence that most major advances in science have not occurred in this manner (16). And, even if

TABLE 1. Steps in the evidence summation process.

Formulate the question
Create definitions and operational rules
Search for the evidence
Include and exclude publications
Summarize and quality score (optional) each publication
Group and combine the evidence
Reach a conclusion
Write research questions

they did, anyone with knowledge of the chaotic landscape of current research will acknowledge that Figure 1 and reality have little in common.

ASSUMPTIONS UNDERLYING THE THEORY OF SYSTEMATIC REVIEWS

Before we accept this model as doctrine, let us consider each step in detail to examine the underlying assumptions (numbers are keyed to the numbered boxes in Fig. 1.).

Development of Questions to Be Examined by the Panel

In this step, the panel decides the specific questions that it wishes to answer. This includes stipulation of the rules (and therefore the assumptions) that the panel will adopt in carrying out its work. The development of these questions is not deductive. It involves the infusion of opinion and belief. There is great danger that framing bias (how one asks the question) will influence the panel's conclusions. For this reason, it is highly desirable for the panel to create an explicit model of the problem and a list of the assumptions and constraints inherent in this formulation (17).

Evidence Collection and Analysis

There are a number of technical problems with this step. Some of these are considered below. The main theoretical problem is that the analyst is typically analyzing a publication rather than the research itself. In doing so, the analyst *assumes* that there is a correspondence between the quality of a publication and the quality of the research that underlies it. Unfortunately, there is little empirical evidence to support this assumption. Given that the skill set required to do unbiased, precise research, and the skill set required to create a high-quality manuscript are relatively distinct, the possibilities for divergence are large. Further complicating this problem is the possibility of abject fraud or more subtle forms of overt or covert spin.

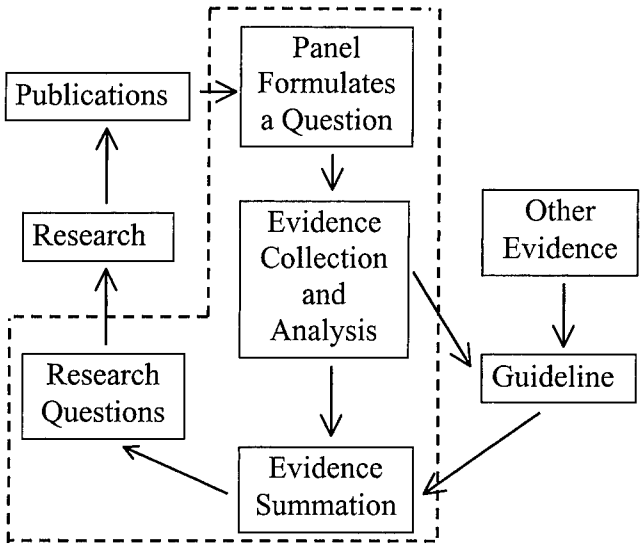


FIGURE 1—Relationship of systematic reviews to guideline development and the advancement of science—a model.

Evidence Summation

Here too, there are a large number of practical problems. There are two major theoretical issues, how to assign weights to the evidence and how to quantitatively combine the evidence. The weights will dictate each publication's influence on the final estimate of the parameter. Weights can be based on the number of subjects in a study, the variance of the responses in a study, a quality score assigned to the study by the panelists, or some combination of these. Unfortunately, we have virtually no knowledge of what system of weighting is most likely to produce unbiased results (15).

Early efforts at quantitative meta-analysis used mathematical models that assumed that all of the studies were conducted under identical circumstances using subjects randomly selected from the same population. With random effects and Bayesian models, these unlikely assumptions are relaxed. Not surprisingly, however, as assumptions are relaxed, confidence intervals get wider, often so wide that the evidence summary produces results consistent with values that span the universe of possibilities (6,11,13,21).

Formulation of Research Questions

Although the deliberate evaluation of evidence certainly provides an inventory of the missing pieces in an evidence model, it by no means leads directly to a research agenda. This is because: a) the number of potential research questions is infinite; b) the process thus necessitates the prioritization of research questions (which ones are worth listing) rather than the creation of questions (a process that could go on forever); c) the evidence summation process provides no information about how to prioritize the questions—prioritization requires judgment and belief quite distinct from the "evidence-based" process; and d) the research questions are typically derived by noting the "holes" in an evidence model, however, because creation of the evidence model is a nonevidence-based act (it requires judgment) the questions that are identified tell us as much about the model as they do about the state of knowledge.

Influence of the Research Questions

Figure 1 implies that the research questions created by evidence panels plays an important role in the selection of research projects. There is no evidence to support this assumption. The influence of research questions developed by

panels pales compared with that of the marketplace ("if we develop a new medication or technology will it generate profit?"), the structure of postdoctoral education (the kinds of questions young investigators are being trained to ask), government funding initiatives, and investigator interest. Thus, there is no guarantee that there will be a systematic attempt to answer the most important questions in a field, even if these questions are correctly explicated by the panel. Consequently, when evidence panels cast their nets to find the crucial evidence, they often pull in empty skeins.

Publication of Research

The model would suggest that all that is researched is published or, said another way, the universe of publications is representative of all of the research that has been done. Unfortunately, it is well documented that studies with positive findings are more likely to be published than those with negative findings (24,26). It is also well known that only a fraction of collected data is ever analyzed or published.

These theoretical limitations are inherent in the evidence evaluation process. They exist regardless of the clinical topic under consideration. They do not invalidate the evidence-based process, so long as the results of each systematic review are accompanied by an acknowledgment of the assumptions and limitations implicit in that review. The panel must avoid the temptation to smooth the rough edges and hide the skewed corners, or else it too will be guilty of wearing the emperor's new clothes.

PRACTICAL PROBLEMS WITH SYSTEMATIC REVIEWS IN EXERCISE MEDICINE

Having considered some of the theoretical problems with systematic reviews, I next consider the practical problems specific to the evaluation of the dose-response relationship of exercise and health outcomes. The focus is on the activities within the dotted box in Figure 1, which are presented in more detail in Table 2.

Formulation of Questions

The panel chose to organize its deliberations around questions generally of the form, "What is the dose response relationship of regular exercise and (fill in the health outcome)." Although this is a very reasonable first approach, it should be recognized that this type of univariate analysis may obscure interactions among the various health outcomes.

The term "dose response to regular exercise" may be too vague. The panel may need to better characterize exactly what it is trying to discover. What is most important? The shape of the dose-response curve over the full range of amounts of exercise, the shape of the curve in a specific range of energy expenditure, the minimal amount of exercise needed to see improvement in a health outcome, or the amount of exercise above which no further improvements are seen?

TABLE 2. Steps for assessing the quality of an evidence evaluation.

Planning
1. Permissible interventions adequately described?
2. Rules for combining interventions developed?
3. Acceptable outcome measures adequately defined?
4. Rules for combining interventions developed?
5. Target population(s) defined?
6. Rules for forcing consensus explicated?
Data gathering
7. Search adequately described?
8. Search technique adequately comprehensive?
9. Any important references missed?
Article selection
10. Inclusion and exclusion criteria adequately described?
11. Inclusion criteria appropriate?
12. Exclusion criteria appropriate?
13. Method for selecting articles adequate?
Article weighting
14. Methods adequately described?
15. Methods reasonable?
Presentation of data
16. Were the data abstracted in a reasonable manner?
17. Are data presented in a coherent format (e.g., an evidence table)?
18. Is the presentation sufficiently detailed?
Article synthesis
19. Methods adequately described?
20. Assumptions of methods clearly stated?
21. Assumptions examined for reasonableness?
22. Sensitivity analyses performed?
Summary
23. Method of reaching consensus described?
24. Limitations of evidence stated and acknowledged?
25. Conclusions in-line with knowledge derived from steps 1 to 17?
Research questions
26. Explanation of how questions are ranked?

Creation of Definitions and Operational Rules

There are a number of definitions and operational criteria that must be worked through before the panel's work may proceed. Items include those listed below:

Methods. What are acceptable methods of measuring exercise? How can studies that use different acceptable methods be combined?

Reporting. What are the minimal requirements for reporting the exercise intervention? Must the exercise be observed or are self-reports acceptable?

Attributes. What characteristics of exercise—duration, intensity, duration × intensity per episode, duration × intensity per week, events per week, etc.—are important? Should intensity be measured on an absolute scale or relative to each individual's capacity? Can two exercise patterns of equal volume (intensity × duration × frequency) be considered equivalent or is there a difference between one hour at half-throttle and one-half hour at full throttle?

Demographics. Does the concept of a single-dose response pattern for both genders, all ages, and all health states make sense, or is it likely that there are distinct curves for subjects in different strata?

Search for the Evidence

MEDLINE searches (even in the best of hands) typically identify only 70–80% of the relevant literature (14,25). Computer searches of other databases, ancestral searches (searching the references cited in each publication), searches

of the file cabinets of experts (admittedly old fashioned, but often very effective), and other techniques may be required to identify more evidence. Whatever the technique, the important questions to ask of these evidence summations are: did they fail to consider important publications and did they fail to screen a foreign language literature that contains important literature?

Including and excluding publications. These criteria will in large part depend on the definitions adopted above (see "Create operational rules. . ."). Studies that fail to adequately characterize interventions or fail to measure outcomes in ways acceptable to the panel will need to be excluded. Randomized control trials (RCTs) are thought to have the highest internal validity but often lack external validity (4,18). Nevertheless, they are often adopted as the sole source of acceptable evidence. The panel should be aware, however, that there is evidence suggesting that RCTs do not hold the trump card on the truth and that the exclusion of all other forms of evidence may be problematic (1,5).

Summarizing (and quality scoring) each article. The Symposium has chosen to work in a disseminated manner in which each participant is given a topic and works in isolation to find and sift through the evidence and prepare a report. Although this strategy has great logistic advantages, careful systematic quality control is needed to ensure the consistency and validity of the final products. The consensus committee will need to carefully evaluate the comprehensiveness and quality of each presenter's literature review. They will also need to ensure that tables or graphics are created that clearly convey the results of the individual studies that were examined. A checklist (Table 2) can facilitate the consensus panel in this task by structuring their critique of each presentation.

Grouping and combining evidence. Apart from the technical challenges of deciding upon a strategy for any quantitative meta-analyses that are attempted, there will likely be a series of "apples and oranges" problems that the panel must work through. These may include the following:

a) The various exercise interventions will need to be grouped according to some set of defined criteria. Operational rules for making these groupings will need to be developed.

b) Similarly, the panel will need to determine whether all studies of the effect of a certain exercise on a health outcome can be pooled or whether age, gender, and baseline fitness status must be considered.

c) There will also be the need to develop rules for combining outcomes. This is true even for seemingly straightforward intermediate outcome measures such as blood pressure. For example, how will three studies of identical exercise interventions in equivalent subject samples be combined when one reports mean change in diastolic blood pressure, one reports the percentage of subjects who achieved a diastolic blood pressure less than 85, and the third reports the percentage of patients whose diastolic BP drops 10 points or more?

Reaching a conclusion. The panel has chosen to study the dose-response relationship of regular exercise to health outcomes, a wise decision because the demonstration that "exercise improves health" fails to provide any guidance regarding the kind and amount of exercise that is needed to reap benefits. With this choice, however, comes a new set of problems. When trying to establish that exercise is beneficial, one need only differentiate among three hypotheses: exercise improves health, exercise has no effect on health, and exercise diminishes health. By disproving the last two, the former can be established by default. When trying to draw a dose response curve, however, there are an infinite number of curves that are *could* explain the data. Although *a priori* knowledge of biological and clinical phenomena may help us exclude many of these curves, the number of viable hypotheses will still be large. It is doubtful that the panel will have sufficient evidence, and thus precision of measurement, to establish that a relationship is of one form (e.g., linear) and not another (e.g., curvilinear). More likely, the panel will have to stop short of establishing a specific dose-response curve and instead describe the family of curves that are consistent with the data and the family of curves that are inconsistent.

Consensus panels also need to decide how they will decide. Namely, they must establish at the outset their rules for establishing agreement or accepting disagreement as inevitable. Must consensus be reached on all questions or can a question be skipped ("There is no evidence," "the evidence is contradictory") or nonconsensus stated ("Four panelists felt that there was moderate evidence for . . .., two found no evidence of . . .")? How will consensus be reached? Will there be voting? Will the voting be private or public? Will some formal system (such as the A,B,C system used by the NHLBI obesity panel) be used to grade the panel's certainty regarding each consensus statement? (2,19) If so, by what process will the letter be assigned?

In this short paper, I have tried to point out some of the assumptions that are inherent in work of this kind. Because there is no one correct way to do this type of work, it is important that the panel be as explicit as possible. It is equally important that the panel acknowledge all of the assumptions and limitations of the analyses. In that way, this work will become a living bridge to future knowledge, rather than a dogmatic tombstone that masks uncertainty and impedes progress by establishing as certain that which is equivocal.

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Type of activity: resistance, aerobic and leisure versus occupational physical activity

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ABSTRACT

HOWLEY, E. T. Type of activity: resistance, aerobic and leisure versus occupational physical activity. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S364–S369. **Purpose:** To define and describe the essential terminology associated with dose-response issues in physical activity and health. **Methods:** Recent consensus documents, position stands, and reports were used to provide reference definitions and methods of classifying physical activity and exercise. **Results:** The two principal categories of physical activity are occupational physical activity (OPA) and leisure-time physical activity (LTPA). OPA is usually referenced to an 8-h d, whereas the duration of LTPA is quite variable. LTPA includes all forms of aerobic activities, structured endurance exercise programs, resistance-training programs, and sports. Energy expenditure associated with aerobic activity can be expressed in absolute terms ($kJ \cdot min^{-1}$), referenced to body mass (METs), or relative to some maximal physiological response (i.e., maximal heart rate (HR) or aerobic power ($\dot{V}O_{2max}$)). The net cost of physical activity should be used to express energy expenditure relative to dose-response issues. The intensity of resistance training is presented in terms relative to the greatest weight that can be lifted one time in good form (1RM). The intensity of OPA followed the guidance of a previous consensus conference. The intensity of most LTPA can be categorized using the standard aerobic exercise classifications; however, for long-duration (2+ hours) LTPA, the classifications for OPA may be more appropriate. **Conclusion:** Physical activities should be classified in a consistent and standardized manner in terms of both energy expenditure and the relative effort required. **Key Words:** METs, % $\dot{V}O_{2max}$, %HRR, %HR_{max}, 1RM, 10-12RM, NET ENERGY EXPENDITURE

There is a great deal of agreement, both from a preventive and a rehabilitative standpoint, that regular participation in physical activity and exercise results in positive health-related outcomes. An important question is, how much is needed to bring about a particular effect? To answer this question, physical activity or exercise interventions must be described in a manner that allows comparisons to be made across the continuum of exercise intensities, types of exercises, and fitness levels. The purpose of this paper is to clarify the various terms associated with physical activity and exercise, and provide guidelines for consistent interpretation of exercise intensity and volume in the context of dose-response issues.

BASIC TERMINOLOGY

The following definitions and descriptions are derived from previous publications in which dose-response issues were paramount (9,10,13,17,28) and from exercise physiology texts (23,30).

Physical activity (PA) is defined as any bodily movement produced by contraction of skeletal muscle that substantially increases energy expenditure. Leisure-time physical activity (LTPA) is a broad descriptor of the activities one participates in during free time, based on personal interests and needs. These activities include formal exercise programs as well as walking, hiking, gardening, sport, dance, etc. The common element is that these activities result in substantial energy expenditure, although the intensity and duration can vary considerably. Occupational physical activity (OPA) is that associated with the performance of a job, usually within the time frame of an 8-h work day. Dose-response refers to the relationship between increasing levels (doses) of PA on changes in the levels of a defined health parameter (e.g., risk factor, disease, anxiety level, and quality of life).

Exercise (or exercise training) is a subcategory of LTPA in which planned, structured, and repetitive bodily movements are performed to improve or maintain one or more components of physical fitness. Detraining describes the physiological, biochemical, and morphological changes after reduction or cessation of exercise training. Overtraining describes a condition in which an individual does more exercise than can be tolerated, resulting in a reduction in performance and a variety of physiological and psychological symptoms.

Aerobic exercise (training) involves large muscle groups in dynamic activities that result in substantial increases in heart rate and energy expenditure. Regular participation results in improvements in the function of the cardiovascular system and the skeletal muscles, leading to an increase in endurance performance. Anaerobic exercise (training) is done at very high intensities such that a large portion of the energy is provided by glycolysis and stored phosphocreatine. Interval training conducted at power outputs well

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beyond an individual's maximal aerobic power, as well as resistance training, are examples of such activities.

Resistance exercise (training) is designed specifically to increase muscular strength, power, and endurance by varying the resistance, the number of times the resistance is moved in a single group (set) of exercise, the number of sets done, and the rest interval provided between sets. Muscular power is a measure of the rate at which work is performed. Muscular strength is a measure of a muscle's ability to generate force. It is generally expressed as maximal voluntary contraction (MVC) for isometric measurements and as the one-repetition maximum (1RM) for dynamic measurements. Muscular endurance is a measure of the ability of a muscle to make repeated contractions against a constant resistance.

Acute health effects or responses of physical activity refer to those positive health-related changes that occur in the hours after a session of physical activity. Chronic (training) effects associated with physical activity occur over time due to changes in the structure or function of various systems, independent of acute effects. There are considerable interindividual differences in responses to structured exercise programs.

Metabolic rate describes the rate of energy expenditure. It is usually estimated by indirect calorimetry, in which measurements of oxygen uptake and carbon dioxide production are used to calculate energy expenditure. Oxygen uptake is converted to kcal, using a constant of 5 $kcal \cdot L^{-1}$, and to kJ by using a constant of 4.19 $kJ \cdot kcal^{-1}$. Resting metabolic rate (RMR) is usually determined with the subject in the supine position, after an overnight fast and 8 h of sleep. An oxygen uptake of 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ is taken as an approximation of the RMR and is considered one MET. Exercise metabolic rate and the caloric costs of activities are determined from oxygen uptake measurements when the subject has achieved a steady state (i.e., the oxygen uptake meets the energy requirement).

Physical fitness is defined as a set of attributes (i.e., cardiorespiratory endurance, skeletal muscle endurance, skeletal muscle strength, skeletal muscle power, flexibility, agility, balance, reaction time, and body composition) that people have or achieve that relate to the ability to perform physical activity. Performance-related fitness is linked typically to those attributes (e.g., power, balance, and reaction time) that are associated with performance outcomes that vary with the sport (e.g., distance running vs weight lifting); however, those same attributes may also be tied to performance in certain occupations. In contrast, health-related fitness focuses on body composition, cardiorespiratory fitness, muscular strength and endurance, and flexibility (a measure of the ability to move a joint through its normal range of motion). Cardiorespiratory fitness reflects the ability of the cardiovascular and respiratory systems to supply oxygen to the working muscles during heavy dynamic exercise. It is usually measured by indirect calorimetry in a laboratory setting as maximal aerobic power or maximal oxygen uptake ($\dot{V}O_{2max}$), which is the highest rate of oxygen uptake achieved during heavy dynamic exercise. However, cardiorespiratory fitness can be estimated accurately from peak power achieved on a cycle ergometer or time on a standard treadmill test, and with somewhat less precision using submaximal tests in which the heart rate response is extrapolated to an age-predicted end point.

Body composition typically describes the amount of fat-free mass (FFM) and fat mass (FM) relative to total body mass. More detailed analyses can characterize bone mass, total body water, etc. Body composition also considers whether body fat is distributed predominately in the limbs or in the trunk; risk of cardiovascular and metabolic diseases is much greater with the accumulation of fat in the abdominal area.

Health is more difficult to define in contrast to the other terms related to dose-response issues. Two previous consensus conferences (9,10) defined health as a human condition with physical, social, and psychological dimensions, each characterized on a continuum with positive and negative poles. Positive health is associated with a capacity to enjoy life and to withstand challenges; it is not merely the absence of disease. Negative health is associated with morbidity and, in the extreme, with premature mortality. This definition was adopted by the Surgeon General's report on Physical Activity and Health (28). For the purpose of examining the role of PA and fitness in a dose-response context, health is described or defined in terms of morbidity or mortality associated with chronic diseases (e.g., coronary heart disease, stroke, and cancer); risk factors or biological markers associated with these diseases (e.g., blood pressure, serum cholesterol, and body fatness); and other outcomes (e.g., quality of life).

PHYSICAL ACTIVITY AND EXERCISE: CHARACTERIZING THE DOSE

The characteristics of intensity, frequency, duration, and mode/type are used to describe the dose of physical activity or exercise needed to bring about a particular response. Frequency is easily described as the number of activity sessions per day, week, or month, and duration typically refers to the number of minutes of activity in each session. Intensity describes, in relative or absolute terms, the effort associated with the physical activity. Intensity is expressed in a wide variety of ways depending on whether it relates to LTPA, resistance training, or OPA. Part of the reason for the variety of expressions is the nature of the activity; the other relates to the time frame over which the activity takes place (i.e., 20–60 min for a fitness workout vs 8 h for a workday).

Leisure-Time Physical Activity

The dose of LTPA can be described in terms of both absolute and relative intensities but, more importantly, in terms of the volume or quantity of energy expended over the course of a day, week, or month. The following sections will expand on each of these characteristics of the dose of LTPA.

Absolute intensity. The absolute intensity of LTPA describes the actual rate of energy expenditure. Common expressions include: oxygen uptake ($L \cdot min^{-1}$), oxygen uptake relative to body mass ($mL \cdot kg^{-1} \cdot min^{-1}$), kcal or kJ per

minute, and multiples of RMR (METs). METs are obtained by dividing the oxygen uptake in $mL \cdot kg^{-1} \cdot min^{-1}$ by 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$. An alternate expression of a MET is 1 $kcal \cdot kg^{-1} \cdot h^{-1}$. These expressions of intensity are important in characterizing the energy expended in an exercise session or over the course of an intervention. The compendium of physical activities developed by Ainsworth et al. (1) has recently been updated in both the number of major headings and the number of specific activities (from 477 to 605) (2). The MET values in the compendium can be used to obtain the absolute energy expenditures associated with all types of physical activities.

Volume of activity. The product of absolute intensity, duration, and frequency yields the total energy expenditure associated with a physical activity over a specified time and is taken as a measure of the volume of PA. Volume may be described in the following units:

Kilocalories. For a 60-kg person doing slow ballroom dancing (3 METs) for 60 min, 3 times per week, the volume is 540 $kcal \cdot wk^{-1}$ for this activity ($3 kcal \cdot kg^{-1} \cdot h^{-1} \times 60 kg \times 3 h \cdot wk^{-1}$). The value would be higher for a heavier person.

MET-min. This is obtained by multiplying the number of minutes an activity is performed by the energy cost in METs. The above example yields 540 MET-min per week ($3 METs \times 180 min \cdot wk^{-1}$). For a 60-kg person, MET-min yields the same value as kcal.

MET-hours. This is calculated by multiplying the number of hours an activity is performed by the energy cost in METs. For the example above, it would be 9 $MET\text{-}h \cdot wk^{-1}$ ($3 METs \times 3 h \cdot wk^{-1}$).

For some dose-response comparisons, it may be important to distinguish between the gross and the net cost of the physical activity. The gross cost of an activity is the total energy expenditure, which includes RMR and the cost of the activity itself. The net cost is that associated with the activity alone. The net cost is obtained by subtracting resting energy expenditure (one MET) from the gross cost. Clearly, for physical activities at the high end of the intensity continuum (i.e., 10+ METs), in which RMR represents 10% or less of total energy expenditure, adjusting the energy expenditure to reflect the net cost will have only a modest impact on overall energy expenditure. On the other hand, when working with activities at the lower end of the intensity continuum, for example, 2–4 METs, adjusting the values to represent the net cost is very important in that RMR might equal 25–50% of total energy expenditure. Failure to make adjustments for these activities will result in an overestimation of energy expenditure associated with the activity and an underestimation of the duration needed to match a comparable net energy expenditure for activities conducted at higher intensities. It is recommended that energy expenditure associated with physical activity be expressed as the net cost to allow for more adequate comparisons across studies in which the rate of energy expenditure can vary greatly. Although the expression of exercise intensity in terms of energy expenditure is very important in terms of the energy cost of the work itself, it does not adequately describe the physiological response demanded of the subject.

Relative intensity. Persons differing in fitness respond in markedly different ways to an exercise challenge set at a fixed absolute intensity. An exercise intensity of 10 $kcal \cdot min^{-1}$ might be a warm-up for one person but require a maximal effort by another. This has been recognized for some time, and exercise physiologists have designed experiments to account for such variation by adjusting the intensity relative to some maximal physiological response. The relative intensity of aerobic activity has been described in terms of percentages of maximal oxygen uptake ($\dot{V}O_{2max}$), oxygen uptake reserve ($\dot{V}O_2R$), heart rate reserve (HRR), and maximal heart rate (HR_{max}). In addition, intensity has been classified relative to the subject's perception of effort, using Borg's Rating of Perceived Exertion (RPE) scale (3,4). These will now be considered in more detail.

Percentage of maximal oxygen uptake ($\dot{V}O_{2max}$). Across a broad range of fitness levels, defined in terms of $\dot{V}O_{2max}$, many physiological responses are normalized by expressing the intensity of exercise as a percentage of $\dot{V}O_{2max}$ ($\%\dot{V}O_{2max}$). This approach was used extensively over the second half of the 20th century in the design of experiments as well as in the development of exercise guidelines, as seen in the American College of Sports Medicine's *Guidelines for Exercise Testing and Prescription* and its position stands. However, in the most recent updates of both of these documents, the relative intensity is also expressed as a percentage of oxygen uptake reserve ($\%\dot{V}O_2$ R) (3,4).

Percentage of oxygen uptake reserve ($\dot{V}O_2R$). $\dot{V}O_2R$ is calculated by subtracting one MET (3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) from the subject's $\dot{V}O_{2max}$. The $\%\dot{V}O_2R$ is a percentage of the difference between resting $\dot{V}O_2$ and $\dot{V}O_{2max}$, and is calculated by subtracting 1 MET from the measured oxygen uptake, dividing by the subject's $\dot{V}O_2R$ and multiplying by 100%. For example, an individual with a $\dot{V}O_{2max}$ of 35 $mL \cdot kg^{-1} \cdot min^{-1}$ who is exercising at 24 $mL \cdot kg^{-1} \cdot min^{-1}$ would be at 65% $\dot{V}O_2R$ ((24–3.5)/(35–3.5)·100%). The $\%\dot{V}O_2R$ corresponds to the heart rate response when it is expressed as a percentage of the HRR (26,27).

Percentage of heart rate reserve (%HRR). The HRR is calculated by subtracting resting HR from maximal heart rate. The %HRR is a percentage of the difference between resting and maximal heart rate, and is calculated by subtracting resting HR from the exercise HR, dividing by the HRR, and multiplying by 100%. Before the most recent ACSM position stand, the %HRR was believed to be closely linked to the $\%\dot{V}O_{2max}$ on a one-to-one basis, that is, 70% HRR = 70% $\dot{V}O_{2max}$. Swain et al. (26,27) pointed out that although this might be the case when vigorous exercise is done by fit individuals, it is not the case for low intensities of exercise, especially when performed by those at the low-end of the fitness scale. For example, a 3-MET activity for someone with a 5-MET maximal aerobic power, is 60% $\dot{V}O_{2max}$ but only 50% of $\dot{V}O_2R$ (2 METs/(5 METs −1 MET)·100%). It has been demonstrated clearly that the %

TABLE 1. Classification of physical activity intensity.

	Endurance-type Activity										Resistance-Type Exercise
	Relative Intensity			Intensity (METs and %$\dot{V}O_{2max}$) in Healthy Adults Differing in $\dot{V}O_{2max}$							Relative Intensity
				$\dot{V}O_{2max}$ = 12 METs		$\dot{V}O_{2max}$ = 10 METs		$\dot{V}O_{2max}$ = 8 METs		$\dot{V}O_{2max}$ = 5 METs	
Intensity	%$\dot{V}O_2R$[a] %HRR	%HR_{max}[b]	RPE[c]	METs	%$\dot{V}O_{2max}$[d]	METs	%$\dot{V}O_{2max}$	METs	%$\dot{V}O_{2max}$	METs	%$\dot{V}O_{2max}$	%1RM[e]
Very Light	<20	<50	<10	<3.2	<27	<2.8	<28	<2.4	<30	<1.8	<36	<30
Light	20–39	50–63	10–11	3.2–5.3	27–44	2.8–4.5	28–45	2.4–3.7	30–47	1.8–2.5	36–51	30–49
Moderate	40–59	64–76	12–13	5.4–7.5	45–62	4.6–6.3	46–63	3.8–5.1	48–64	2.6–3.3	52–67	50–69
Hard	60–84	77–93	14–16	7.6–10.2	63–85	6.4–8.6	64–86	5.2–6.9	65–86	3.4–4.3	68–87	70–84
Very Hard	≥85	≥94	17–19	≥10.3	≥86	≥8.7	≥87	≥7.0	≥87	≥4.4	≥88	≥85
Maximal	100	100	20	12	100	10	100	8	100	5	100	100

Modified from Table 1 of ACSM Position Stand (ref. 5).
[a] %$\dot{V}O_2R$ - percent of oxygen uptake reserve; %HRR - percent of heart rate reserve.
[b] %HR_{max} = 0.7305 (%$\dot{V}O_{2max}$) + 29.95 (ref. 20); values based on 10-MET group.
[c] Borg Rating of Perceived Exertion 6–20 scale (ref. 8).
[d] %VO_{2max} = [(100%-%$\dot{V}O_2R$) MET_{max}^{-1}] + %$\dot{V}O_2R$; personal communication (D. P. Swain, 2000).
[e] RM = repetitions maximum, the greatest weight that can be moved once in good form.

$\dot{V}O_2R$ is numerically identical to the %HRR across the fitness continuum.

Percentage of maximal heart rate (%HR_{max}). Because of the linear relationship between HR (above ~110 b·min^{-1}) and $\dot{V}O_2$ during dynamic exercise, investigators and clinicians have long used a simple percentage of maximal HR (%HR_{max}) as an estimate of the %$\dot{V}O_{2max}$ in setting exercise intensity (15,18).

The rating of perceived exertion (RPE). The RPE is not viewed as a substitute for prescribing exercise intensity by HR, but once the relationship between the heart rate and RPE has been established, RPE can be used in its place (5). However, the RPE may not consistently translate to the same intensity for different modes of exercise, so one should not expect an exact matching of the RPE to a %HR_{max} or %HRR (3).

The categories of exercise intensity must consider the time frame over which an activity takes place. The ACSM's position stand classifies intensity of aerobic activities based on a duration of up to 60 min. To review the literature in a consistent manner with regard to the issue of exercise intensity, one must be able to equate intensity across all of the expressions mentioned above. Table 1 shows the categories of exercise intensity as described in the ACSM position stand, with %$\dot{V}O_2R$ and %HRR used to set the standard for the other expressions of exercise intensity (3). These are shown on the left side of the table with intensities ranging from very light to maximal. The RPE values are based on Borg's 6–20 RPE scale (8).

Taking the lead from the earlier consensus conferences on exercise, fitness and health (9,10), the Surgeon General's report and the most recent ACSM position stand included absolute MET values for groups differing in $\dot{V}O_{2max}$. Table 1 provides the absolute exercise intensities (in METs) for each of the intensity classifications for four groups that vary in $\dot{V}O_{2max}$. On average, $\dot{V}O_{2max}$ decreases with age, and is lower in women, compared with men, across age. The 50th percentile values for $\dot{V}O_{2max}$ (in METs), based on the Canada Fitness Survey (12), are shown in Table 2.

The difference between the %$\dot{V}O_{2max}$ and the %$\dot{V}O_2R$ in Table 1 is inversely related to a person's $\dot{V}O_{2max}$. For example, one MET represents 20%, 10%, and 5% of $\dot{V}O_{2max}$ values of 5, 10, and 20 METs, respectively. For those at the high end of the fitness continuum, there is little difference between %$\dot{V}O_2R$ and %$\dot{V}O_{2max}$ values; however, the difference is considerable at lower intensities for those with low fitness levels. The %$\dot{V}O_2R$ was converted to %$\dot{V}O_{2max}$ using the following equation (Swain, D. P. Conversion of percent $\dot{V}O_2$ reserve to percent $\dot{V}O_{2max}$, personal communication, 2000):

$$\%\,\dot{V}O_{2max} = \{(100\% - \%\dot{V}O_2R)\,MET_{max}^{-1}\} + \%\dot{V}O_2R \quad (1)$$

The MET values listed for each fitness level equal the stated %$\dot{V}O_{2max}$ and %$\dot{V}O_2R$ values.

The %HR_{max} values listed in Table 1 were derived from an equation by Londeree and Ames (20):

$$\%HR_{max} = 0.7305\ (\%\dot{V}O_{2max}) + 29.95. \quad (2)$$

This equation is similar to those of Swain et al. (25) and Hellerstein and Franklin (18). There was little difference in the %HR_{max} values calculated by the above equation across the four fitness groups for each of the intensity classifications, so the %$\dot{V}O_{2max}$ values for the 10-MET fitness group were used to provide the %HR_{max} values for Table 1.

Table 1 allows an investigator to classify data on exercise intensity in a consistent manner, whether expressed in oxygen uptake (METs), heart rate, or ratings of perceived exertion. However, it is clear that if one uses a fixed metabolic rate (i.e., METs) to define an intensity category, the relative intensity changes dramatically as one moves across the fitness continuum. This was recognized in both of the earlier consensus conferences (9,10), as well as in the Report of the Surgeon General (28), and is addressed in Shephard's presentation in the conference (24). Figure 1, based on a graph by Haskell (16), shows why one must use caution when interpreting an absolute intensity of exercise as being

TABLE 2. 50th percentile values (in METs) for $\dot{V}O_{2max}$.

Age (yr)	20–29	30–39	40–49	50–59	60–69
Male	12.3	12.3	10.9	9.7	8.0
Female	10.0	9.1	8.0	7.4	6.3

Based on data from the Canada Fitness Survey (12).

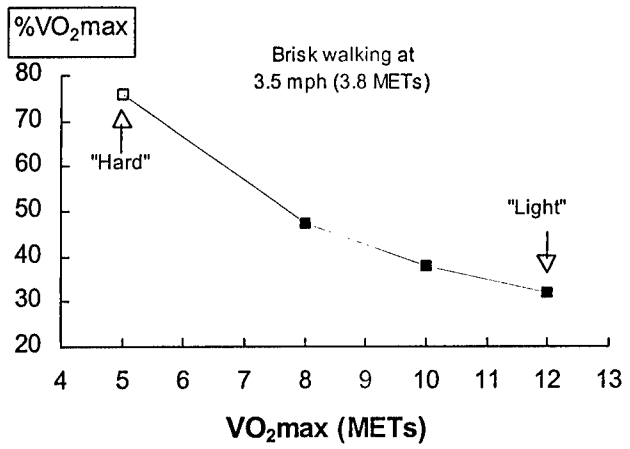


FIGURE 1—Changes in the relative intensity of exercise ($\%\dot{V}O_{2max}$) when the same absolute intensity of exercise is performed by groups differing in $\dot{V}O_{2max}$. Figure adapted from Haskell (16).

"moderate" when it is applied to individuals differing in cardiorespiratory fitness. The 3.8-MET activity identified in Figure 1 represents a range of relative intensities of 32–76% $\dot{V}O_{2max}$ for the fitness groups described in Table 1. The range of 3–6 METs was identified as representing "moderate physical activity" in the original CDC/ACSM recommendation when "most healthy adults" were used as the reference point (22). This same range of absolute exercise intensities represents higher relative intensities when applied to older, less fit, individuals.

Occupational Physical Activity

In contrast to the 60-min time frame over which the categories of intensity were developed for aerobic activities, the time frame for occupational physical activity is the 8-h day. Montoye et al. (21) have recently reviewed the different approaches that have been used to obtain information about occupational physical activity. In 1994, Bouchard and Shephard (9) provided a classification scheme, based on the work of Brown and Crowden (11), that can be used to classify the relative intensity of occupational physical activity (see Table 3). Some studies use the compendium of physical activity to assign MET values for specific occupational settings to obtain the energy expenditure associated with the OPA (2).

Resistance Training

The terminology used to describe the dose of resistance exercise needed to bring about a particular response is somewhat different from that used for aerobic exercise. "Intensity" refers to the amount of resistance; "repetitions" or "reps" defines the number of times a weight is lifted or a resistance is moved; and a "set" describes the number of times the desired number of repetitions is performed. Some use the product of the reps, sets, and resistance to obtain a measure of the volume of exercise done in a workout (7,14).

The counterpart to $\dot{V}O_{2max}$ in resistance training is the one repetition maximum (1RM), the greatest weight that can be lifted one time in good form. Once this value is known for each exercise, the intensity can be set at a percent of the 1RM value

TABLE 3. Intensity of occupational work.

Intensity	Energy Expenditure ($kJ \cdot min^{-1}$)	Energy Expenditure (METs)
Sedentary	<8.4	<1.9
Light	8.4–14.7	1.9–3.3
Moderate	14.8–20.9	3.4–4.7
Heavy	21.0–31.4	4.8–7.1
Very heavy	>31.4	>7.1

From Bouchard and Shephard (9) based on data from Brown and Crowden (11). MET values based on mean body weight of 63 kg, from Brown and Crowden (11).

(like a percent of $\dot{V}O_{2max}$ for aerobic exercise). In much the same way that the duration of aerobic exercise is inversely related to intensity, the number of repetitions a person can perform is inversely related to the %1RM. For example, the following are typical estimates of the number of repetitions that can be done at a fixed percentage of 1RM: 95%: 2–3; 90%: 4; 85%: 6; 80%: 8–10; and 75%: 10–12 (6). Because of this inverse relationship between %1RM and the number of repetitions, intensity can also be defined as a specified RM, that is, doing one set of 10–12 RM. However, due to the variability in the number of repetitions that can be done at the same %1RM for different muscle groups (e.g., bench press vs leg curl), and between trained and untrained subjects, these estimates are simply guidelines, rather than hard and fast rules (19).

The intensity and volume of exercise in a resistance-training program can be adjusted by changing the weights or resistance, the repetitions per set, the number of sets, and the rest periods between sets (5,14). The ACSM position stand provides guidance in the classification of exercise intensity for resistance training. The classification is based on 8–12 repetitions for persons under 50–60 yr, and 10–15 repetitions for persons older than 50–60 yr. The ACSM listed relative intensity values for resistance-type exercise as a percent of maximal voluntary contraction (MVC), a measure of maximal isometric strength. This term was used interchangeably with 1RM, and Table 1 reflects this change.

Research Directions

The intensity of aerobic physical activity is defined within a 60-min time frame, whereas the intensity of occupational activity is viewed over 8 h. There are a wide variety of activities that fall between these two extremes of duration (e.g., prolonged hikes and gardening activities), and there is a need to determine how one might classify intensity in these cases. For occupational activities involving lifting, the limits of energy expenditure have been set on the basis of both duration and the height of the lift. For example, the National Institute for Occupational Safety and Health has set the limit of energy expenditure at 2.2 $kcal \cdot min^{-1}$ (9.2 $kJ \cdot min^{-1}$) for frequent lifting over a vertical distance greater than 75 cm that is carried out for 2–8 h (29). These analyses should be considered in future reviews of the relative intensity of OPA.

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Quantifying energy expenditure and physical activity in the context of dose response

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ABSTRACT

LAMONTE, M. J., and B. E. AINSWORTH. Quantifying energy expenditure and physical activity in the context of dose response. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S370–S378. **Purpose:** Methods for assessing physical activity (PA) and energy expenditure (EE) were reviewed to identify potential limitations to evaluating and interpreting dose-response relationships between PA and health-related outcomes and to suggest future research directions in this area. **Methods:** Literature describing PA and EE assessment methodology was reviewed according to the reported validity, reliability, and feasibility of the measurement in epidemiologic studies. A summary of this review is presented for techniques applicable to studying PA or EE among free-living individuals. **Results:** Several methods with varying degrees of precision and feasibility have been used to assess PA and EE in free-living populations. Lack of a gold standard field measure of PA may explain some of the variability in precision among these methods. The most accurate field measure of EE appears to be doubly labeled water; however, this approach has limited feasibility in terms of cost and use in studies of total EE only. Electronic motion sensors and physiologic measures related with EE are limited in their ability to discriminate specific types of PA and by inconvenient measurement procedures. Self-reported PA records and surveys are low-cost, relatively unobtrusive methods of assessing PA and EE in field settings and vary in terms of their format, mode of administration, and degree of detailing habitual PA levels. Disparity in the metric used to quantify PA and EE exists within the current literature, which limits the interpretation and comparison of observed dose-response relationships. **Conclusions:** Efforts to develop equated methods of assessing PA and EE in free-living populations are needed before a systematic evaluation and interpretation of dose-response characteristics between PA and specific health-related parameters can be undertaken.

The health benefits of regular physical activity (PA) are well established (10,17,73,86); however, the precise amount and type of PA required to achieve specific health-related outcomes remains unclear (36). To accurately understand a specific dose-response relationship, valid and reliable measures of the exposure and outcome of interest must exist. Population-based studies of PA and health typically rely on binary outcome measures, such as mortality (19) or nonfatal incident disease (38), which enhances the accuracy of measuring the study outcome. Because PA is a complex and multidimensional exposure variable, population-based measurement is difficult. The need for precise quantification of activity levels and energy expenditure (EE) among free-living people has been well documented (8,36,50,54,66,68,86,88,94). Lack of a gold standard measure of PA has confounded the development of a universally accepted field assessment technique. Consequently, several methods of assessing PA and EE exist along a continuum of accuracy and feasibility (54,86). Each method has strengths and limitations for its use in observational epidemiologic studies of PA and health-related outcomes. In this paper, we will: 1) present methods used to quantify PA and EE; 2) identify potential measurement-related limitations to evaluating the dose-response of PA for health-related outcomes; and 3) identify research priorities to advance our current understanding of dose-response issues in PA and health-related research. Emphasis will focus on methods used to assess PA and EE in epidemiologic studies of PA, EE, and health-related outcomes among free-living individuals.

CONCEPTUAL FRAMEWORK FOR QUANTIFYING ENERGY EXPENDITURE

Conceptual Framework

Two important aspects of measuring PA and EE are the definition and application of terms related with PA. Detailed definitions of relevant terms have been presented by Howley (42). It is important to recognize that PA and EE are not synonymous terms. PA is a behavior that results in EE and is typically quantified in terms of its frequency (number of bouts) and its duration (e.g., minutes per bout). EE reflects the energy cost or intensity associated with a given PA. It is a direct function of all metabolic processes involved with the exchange of energy required to support the skeletal muscle contraction associated with a given PA. Although several factors may influence EE on a relative scale (e.g., age, body size, fitness level), if one assumes a fairly constant human mechanical efficiency to perform physical

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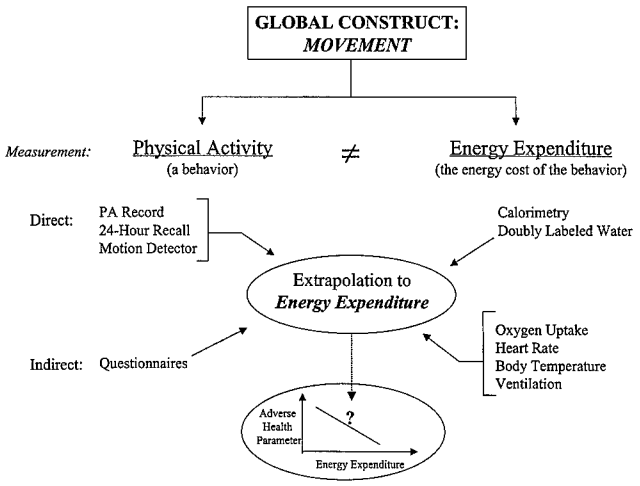


FIGURE 1—A conceptual model of the relationships between movement, physical activity, and energy expenditure, as well as methods of assessment.

work, then absolute EE is generally constant for a given PA (2,68). Clearly defining and standardizing terms associated with PA measurement is a critical step in reducing unwanted sources of variation, producing unbiased estimates of the exposure, and facilitating meaningful data interpretation and comparison with data from other populations (36,43,68).

The construct representing the exposure variable within the activity-health paradigm might best be defined as "movement," with two dimensions: PA (a behavior) and EE (the energy cost of the behavior) (Fig. 1). Direct and indirect measures exist for both PA and EE. However, because recent evidence suggests that EE may be more predictive of health-related outcomes than the specific type of PA that results in the expended energy (55,62), researchers often extrapolate measures to units of EE before analyzing potential effects on health parameters. In epidemiologic studies of PA and health, EE is frequently estimated from PA questionnaires or other indirect measures that reflect patterns of PA in various settings. Indirect measures of PA or EE may provide acceptable estimates of EE, depending on the degree of concordance with direct measures of EE. Day-to-day intra-individual variation in PA has been shown to affect the precision of both direct and indirect measures of PA and EE (35,56) and, therefore, must be considered when choosing a method of PA assessment. Table 1 presents a comprehensive list of methods used to measure PA and EE. These

TABLE 1. Methods of assessing physical activity or energy expenditure.

Direct
Observation
Room calorimetry (e.g., body heat production)
Doubly labeled water
Biomechanical forces
Acceleration vectors (e.g., accelerometry)
Motion sensors (e.g., pedometry)
PA records or diaries, recall interviews
Indirect
Indirect calorimetry (e.g., O_2 uptake, CO_2 production)
Physiologic measures (e.g., heart rate, ventilation, temperature, estimated cardiorespiratory fitness)
PA surveys or questionnaires
Surrogate reports (e.g., energy intake)

methods have been described in detail by others (8,13,30,54,66,68,88,94). The following review is delimited to direct and indirect techniques that can be used to assess PA and EE among free-living populations. The utility of objective laboratory procedures (e.g., calorimetry) for measuring EE and validating field techniques for assessing PA, however, should not be understated.

Direct Method of Assessing PA and EE

Doubly labeled water (DLW). The DLW method has been used to assess human EE under laboratory and field conditions (59,68,83). The estimation of EE with DLW is based on the rate of metabolic CO_2 production ($\dot{V}CO_2$) (83). DLW consists of the stable water isotopes ^2H_2O and $H_2{}^{18}O$, and is administered to subjects as a liquid that is dosed according to body size. Urinary excretion of these isotopes in the form of water and CO_2 is tracked with mass spectrometry over several days, and oxygen uptake ($\dot{V}O_2$) and EE are extrapolated from $\dot{V}CO_2$ using established equations (83). Although DLW provides precise estimates of free-living EE, this technique is expensive, is limited to studies of total EE, and does not differentiate the duration, frequency, or intensity of specific PA.

Motion detectors. Motion detectors are mechanical devices worn on the body to quantify EE under the assumption that movement (or acceleration) of the limbs and torso is closely related with whole body EE (13,30,37). Simple pedometers are used to quantify ambulation in terms of steps·unit time^{-1} (e.g., per day) but are limited by issues pertaining to device calibration and the inability to differentiate type, frequency, duration, and intensity of specific PA (8,13,66). Uniaxial (e.g., Caltrac, CSA) and triaxial (e.g., Tri-Trac) accelerometers measure the rate and magnitude of which the body's center of mass displaces during movement. Although data from accelerometers can be used to assess frequency, duration, and intensity of PA, the specific type of PA is unknown. The EE owed to activities involving the extremities or increased resistance to body movement (e.g., uphill walking) is not well accounted for (37). Large discrepancies have recently been reported among existing accelerometer cutpoints for estimating the energy cost of lifestyle PA under free-living conditions (1,91). Subject compliance issues, potentially altered PA patterns, and the cost of the more sophisticated instruments limit the practicality of using motion detectors to measure PA and EE in large studies of free-living individuals.

PA records, logs, and recalls. PA records are ongoing diaries kept by individuals that attempt to capture all sources and patterns of PA during a defined time frame (4,8). Their level of detail ranges from recording each activity and its associated duration (4) to recording activities performed at specified time intervals (e.g., every 15 min) (18). PA records may be limited in population studies because of the intensive effort required by the participant and study staff. Similar to PA records, PA logs aim to provide a detailed account of habitual daily activities and their associated duration (7,8). Unlike the diary format of the PA

record, however, the PA log is structured as a checklist of specified activities usually developed from population-specific PA focus groups (4). PA logs may be more convenient to complete and process than PA records. Alternatively, PA logs may be of limited value if participants engaged in activities other than those listed on the log. PA recalls are typically interviews (telephone or in person) aimed at detailing an individual's PA level during the past 24 h or longer (8,54,64). Multiple random 24-h PA recalls conducted via telephone interviews have recently been used in an effort to minimize the influence of response bias and altered participant activity patterns during assessment (64). Time requirements and the specified recall time frame may limit the use of PA recalls in large epidemiologic studies. For the PA record, log and recall, multiplying the duration of each activity by its corresponding intensity in METs (2,3) yields an estimate of EE (e.g., MET-min·d^{-1}) that can be computed as total EE, or as categories of light, moderate, and vigorous intensity PA (73). PA records, logs, and recalls provide much detail on the type and pattern of PA. However, issues related with individual recall ability, response bias (recall bias, social desirability bias), and the potential for altered PA patterns or poor compliance while completing the PA records or logs may limit their use for population-based assessment of PA or EE.

Indirect Method of Assessing PA and EE

Oxygen uptake ($\dot{V}O_2$). Development of small portable indirect calorimeters (e.g., Cosmed K4 b^2) has recently allowed for field assessment of $\dot{V}O_2$ (39,91), from which EE can be estimated based on assumed relations between $\dot{V}O_2$ and the caloric cost of substrate oxidation (20,29,68). However, issues pertaining to costs, cumbersome and obtrusive instrumentation, altered patterns of PA, and the lack of well-established validity and reliability in a variety of field settings limit the usefulness of this approach to quantifying EE in population-based studies of PA and health.

Heart rate (HR). Estimates of EE have been made from HR based on the assumption of a strong linear relation between HR and $\dot{V}O_2$ (25,59). Although the HR–$\dot{V}O_2$ relationship is linear over a wide range of PA intensities, this is frequently not the case during low and very high intensity activity (30). Because many daily activities are low to moderate intensity (2,3), HR monitoring may not provide precise estimates of daily EE among free-living individuals. Additional issues such as developing individual HR–$\dot{V}O_2$ calibration curves to accurately estimate EE, and the variety of ancillary factors that affect HR (e.g., stress, body temperature, and medication) make HR monitoring a less suitable surrogate of PA or EE in health-related research. HR monitoring, however, may be useful as part of an integrated multisystems approach to population-based PA and EE assessment (37,40).

Body temperature. A close relationship between core body temperature (BT) and EE has been reported under laboratory conditions (15). However, this approach to estimating EE may be impractical due to a time delay ($\approx$ 40 min) before a steady-state BT has been achieved and an accurate estimate of EE can be made. Further, the BT-EE relationship is altered by hot and humid climates and by fitness level. Measurement of BT is inconvenient under most circumstances. Therefore, BT monitoring is not suitable as a single measure of EE among free-living individuals but might be useful as part of an integrated monitoring system (40).

Ventilation ($\dot{V}_E$). Because of the close relationship between $\dot{V}_E$ and $\dot{V}O_2$ (25), continuous monitoring of $\dot{V}_E$ may be attractive for assessing EE. However, similar limitations to field assessment of $\dot{V}_E$ exist as were described for $\dot{V}O_2$. Recently, an electronic device worn around the thorax to detect ventilatory responses to PA has been proposed as a method of assessing EE in free-living conditions (40). Separately or as part of an integrated model, this application may enhance field estimations of EE; however, this procedure is still in its developmental stages, and data are not yet available to establish its accuracy, reproducibility, and feasibility as a surrogate measure of EE.

PA questionnaires. Self-report questionnaires are used most frequently to assess PA and EE in large-scale epidemiologic studies of health-related outcomes (Table 2). PA questionnaires are classified as global, recall, and quantitative history instruments based on their level of detail and subject burden (54,68). Global questionnaires are short one- to four-item surveys aimed at general levels of PA. Although they are easy to complete, global surveys provided limited information on specific types and patterns of PA and result in only simple PA classifications (e.g., active vs inactive) (14,81). Recall questionnaires typically have 10–20 items and allow fairly specific assessment of frequency, duration, and types of PA during the past day, week, or month. Compared with the global survey, recall instruments are somewhat more complex and burdensome to complete; however, the PA assessment is more detailed. Scoring systems vary among recall questionnaires, ranging from simple ordinal scales (e.g., 1-5, low to high PA) (9,11,61), to unitless summary indices (e.g., exercise units) (47,65,80), to a summed score of continuous data (e.g., MET-min·d^{-1}) (7,16,71). The advantage of the latter measure is the ability to evaluate dose-response relationships across categories of light, moderate, and vigorous PA or EE according to published recommendations (73,86). Quantitative histories generally have more than 20 items, are very detailed, and typically reflect the volume (e.g., frequency and duration) of leisure-time or occupational PA obtained in the past year or through a lifetime. PA scores are usually expressed as a continuous variable (e.g., kcal·kg^{-1}·wk^{-1}) (6,51,72,85), which allows for categorical evaluation of dose-response effects on health parameters based on recommended EE cutpoints (e.g., $\geq$ 14 kcal·kg^{-1}·wk^{-1}) (86). Though concerns about the limitations of human recall and report bias are valid (12,28,56), PA questionnaires provide a relatively easy, inexpensive, and nonreactive method of assessing PA or EE in large free-living populations.

ISSUES IN QUANTIFYING PHYSICAL ACTIVITY AND ENERGY EXPENDITURE

The objective of epidemiologic research is to produce an unbiased estimate of the strength of association between PA and a specific health outcome, and to determine whether adequate evidence exists in support of a causal relationship. Demonstrating that higher levels of PA or EE result in a graded effect in a defined health parameter is an important piece of evidence for causality. Several issues pertaining to the evaluation of a potential dose-response relationship should be considered to allow for accurate interpretation and application of the data.

Table 3 lists potential limitations to evaluating and interpreting the dose-response characteristics between PA or EE and health-related outcomes. Two very important considerations are clearly defining whether PA *or* EE is the exposure variable and attempting to examine the dose effect of exposure variables that have been quantified in different summary units. The latter point can be seen by comparing PA and all-cause mortality data among men in the British Regional Heart Study (89) and the Harvard Alumnus Health Study (71), which used different summary units to express PA and EE (Table 2). Both studies generally supported a strong graded inverse association for PA and EE with total mortality. The Harvard study showed about a 40% reduction in age-adjusted mortality at an EE of about 1500 kcal·wk^{-1}, whereas the British study showed a similar reduction in age-adjusted mortality at a PA level defined as "occasional." Not only does categorizing PA levels as a unitless index in the British study prevent cross-population comparison of the dose-response observed in the two studies, it is also very difficult to form a recommendation from the British data on the amount of PA required to reduce the risk of mortality in middle-aged men. For this reason, instruments used to assess PA should yield measures in units of EE or should allow for easy conversion of PA dimensions (e.g., frequency and duration) to units of energy expenditure (e.g., MET-min·d^{-1}).

Recent attention has focused on the inappropriate use of ordinal scales and summary indices to evaluate PA effects that are based on assumptions of interval or ratio level data (96,97). Some PA questionnaires are scaled on an ordinal rather than linear metric. Because the size of the increment between the levels of PA or EE (e.g., sedentary, active, highly active) is not equal, the true meaning of ordinal scores may not be of equal physiological value between one level of EE to another. Consequently, evaluation of the true underlying dose-response between PA and a defined health outcome might be compromised. Further, if two separate PA instruments have nonequated measurement units, it is likely that nonequivalent PA or EE summary scores will result, and cross-population dose-response comparisons will be meaningless. New measurement scaling/calibration methods (e.g., Rasch modeling techniques) (57,96,97) can be employed to transform ordinal scales into an equated linear metric before using them in research. Other issues are construct and item bias (e.g., the PA domains have different cross-population meaning), and method bias (cross-population disparity in survey characteristics or administration). Failure to account for these potential sources of measurement error could make examining and interpreting cross-population dose-response characteristics essentially like comparing apples and oranges. Additionally, questionnaires must reflect the types of habitual PA that are performed in the target population (4,7,9,43). This issue has recently been highlighted by an expert panel on measuring PA among women and minorities (63) and may account for the discrepant findings between PA and certain health-outcomes reported among women (79,86,92).

Choosing the proper cutpoints for categorical dose-response analysis of continuous measures of PA or EE is problematic. Cutpoint bias (34) occurs when dose-response cutpoint levels are assigned to maximize the desired effect (e.g., statistical significance, magnitude of effect, or data trends) or are fit to the population-specific data distribution (e.g., sample tertile cutpoints). A more appropriate and standardized method might be to assign cutpoints based on published physiologic thresholds associated with health-related outcomes (e.g., Surgeon General's Report recommendation of $\geq$ 150 kcal·d^{-1} vs $<$ 150 kcal·d^{-1}) (86). To reduce the potential of cutpoint bias and to provide a more precise dose-response evaluation based on the true characteristics of the data, Greenland (34) recommends alternative analytic methods for assessing the nature of dose-response relationships with continuous data as opposed to creating an ordinal scale for linear modeling. Furthermore, because the specific nature of the dose-response curve (e.g., monotonic, asymptotic, or polynomial) may vary across the spectrum of health parameters related with PA, equivalence between units used to categorize PA or EE, use of physiological thresholds to form EE categories, and alternative approaches for evaluating dose-response characteristics may lead to a more meaningful consensus on the true dose of PA required to achieve specific health-related outcomes.

Finally, little is known about the process of recalling (e.g., perceiving, encoding, storing, and retrieving) past levels of PA (12,28). Several reports have supported stronger associations with health-related outcomes for vigorous rather than nonvigorous PA (86), which may reflect a bias in accurately recalling activities of different intensity (28,43,64). Additionally, it appears that several factors related with the recall instrument and the subject (e.g., question context and age, respectively) modify the accuracy of PA recall (28). Because recall methods are the most common approach to assessing levels of PA and EE in large epidemiologic studies, understanding how PA recall processing occurs and whether this process can be enhanced deserves more attention.

FUTURE RESEARCH PRIORITIES

Based on our evaluation of the field methods used to measure PA and EE, the limitations in current analytic approaches to assessing dose response, and the limited understanding of the process involved in PA recall, the following recommendations for future research are made:

1) Develop a gold standard field measure of PA.

TABLE 2. Self-report methods and cut-points used to quantify levels of physical activity and energy expenditure in free-living populations.

Method/Questionnaire[a]	Type of Activity[b]	Expression of Dose-Response[c,d]	Author (Reference)
General recommendations			
CDC-ACSM	JOB, EX, SP, LEIS, TRAN, HH	Light Moderate (3–6 METs) Vigorous (6 METs)	Pate et al., 1995 (73)
ACSM	EX, SP, LEIS	Very light (<20% HRR*) Light (20–39%) Moderate (40–59%) Hard (60–84%) Very hard (≥85%) Maximal (100%)	ACSM, 1998 (10)
Surgeon General Report	JOB, EX, SP, LEIS, TRAN, HH	≥150 kcal · d^{-1} or 1000 kcal · wk^{-1}	USDHHS, 1996 (86)
Global			
St. Louis Heart Health	EX	No, yes	Schechtman et al., 1991 (77)
NHIS	TOTAL (relative to peers)	Less, same, more	Slater et al., 1987 (82)
NSPHPC	TOTAL (relative to peers)	Much less, somewhat less, same, somewhat more, much more inactive, active	Slater et al., 1987 (82) Belloc and Breslow, 1972 (14)
Adventist Mortality	EX (work or play)	Inactive, moderately active, highly active	Lindsted et al., 1991 (58)
Parental Report	TOTAL	Sedentary, slightly active, active	Murphy et al., 1988 (70)
Finnish	JOB, LEIS	Low, high	Salonen et al., 1982 (76)
NHANES I	EX NON-EX	Little, moderate, much, quite inactive, moderately active, Very active	Slater et al., 1987 (82)
Lipid Research Clinics	JOB, EX JOB, NON-JOB, EX	Inactive, active, very low, low, moderate, high	Siscovick et al., 1988 (81) Ainsworth et al., 1993 (5)
Godin Leisure Time	EX, SP, LEIS	Strenuous, moderate, light, total, sweat inducing	Godin et al., 1985, 1986 (32,33)
MN Heart Health	JOB, LEIS	5-point ordinal indices MET-min · d^{-1}	Jacobs et al., 1986 (45) Jacobs et al., 1993 (43)
HIP	JOB, NON-JOB, TRAN TOTAL	I (least), II, III, IV (most); light, intermediate, heavy	Shapiro et al., 1965 (78)
NHIS/HPDP	JOB, LEIS	Sedentary (0.1–1.4 kcal · kg^{-1} · d^{-1} Moderately active (1.5–2.9 kcal · kg^{-1} · d^{-1}) Very active (≥3 kcal · kg^{-1} · d^{-1}) Sedentary, irregularly active, regular but not meeting 1990 objective, regular and meeting 1990 objectives	Weiss et al., 1990 (90)
Alameda County	EX, SP, LEIS	Tertiles based on 12-point ordinal scale	Kaplan et al., 1996 (48)
Goteborg PA	JOB, EX, LEIS	4-point ordinal scale	Johansson et al., 1988 (46)
Framingham Usual	JOB, LEIS	Sedentary, slightly active, moderately active, heavy activity based on a unitless index	Kannel and Sorlie, 1979 (47)
Stanford Usual	EX, LEIS	Moderate activity, ordinal scale = 0–6 Vigorous activity, ordinal scale = 0–5	Sallis et al., 1985 (75)
Honolulu Usual	JOB, EX, LEIS, YRD	Inactive, moderate, active based on a unitless index	Donahue et al., 1988 (27)
British usual	SP, LIES, YRD	Inactive, light, moderate, moderate-vigorous based on a unitless index	Wannamethee et al., 1998 (89)
Recall questionnaires			
Seven-day recall	EX, LEIS	Light (1.0–2.9 METs) Moderate (3.0–5.0 METs) Hard (5.1–6.9 METs) Very hard (≥7 METs) kcal · kg^{-1} · d^{-1}	Sallis et al., 1985 (75) Blair et al., 1985 (16)
CARDIA 7-day recall	JOB, EX, LEIS	Light (1.5 METs) Moderate (4.0 METs) Hard (6.0 METs) Very hard (10.0 METs) kcal · kg^{-1} · d^{-1}	Sidney et al., 1991 (80)
Baecke	JOB, SP, LEIS	Ordinal indices (1–5) for work, leisure, and sport	Baecke et al., 1982 (11) Jacobs et al., 1993 (43)
ARIC/Baecke	JOB, SP, LEIS JOB SP, LEIS	Ordinal indices (1–5) for work, leisure, and sport	Jacobs et al., 1993 (43) Ainsworth et al., 1993 (6) Richardson et al., 1995 (74)
Magnus	EX, LEIS	4-point ordinal scale 2-point nominal scale	Magnus et al., 1979 (61)
ACLS 7-day recall	EX, SP, LEIS	Summary index in MET-h · wk^{-1}	Kohl et al., 1988 (49)
British Civil Servants	SP, LEIS	2-point nominal scale	Morris et al., 1980 (69)
Zutphen	JOB, SP, LEIS	Light ($^{-1}$ · hr^{-1}) Moderate (2 to $^{-1}$ · hr^{-1}) Heavy (≥ 4 kcal · kg^{-1} · hr^{-1}) 4-point ordinal scale	Caspersen et al., 1991 (23)
Liverpool LTPA	EX, LEIS	Moderate (3–4.9 METs) Hard (5–6.9 METs) Very hard (≥7 METs) kcal · d^{-1}	Lamb and Brodie, 1991 (53)
BRFSS-1985	EX, LEIS	0, 0.1–2.9, and ≥3 kcal · kg^{-1} · d^{-1}	White et al., 1987 (93)
BRFSS -2000	JOB, EX, SP, LEIS, HH, CARE	Inactive, insufficiently active, regularly active	Macera and Pratt, 2000 (60)
College Alumnus	EX, SP, LEIS	2, 3, and 8-point ordinal indices in kcal · wk^{-1}	Paffenbarger et al., 1986 (71)
Bouchard 3-d record	JOB, SP, LEIS	9-point ordinal scale, kcal · d^{-1}, kcal · kg^{-1} · d^{-1}	Bouchard et al., 1983 (18)
Nurses Health Study	EX, LEIS	Summary index of MET-h · wk^{-1}	Wolf et al., 1994 (95)
Male Health Professionals	EX, LEIS	Summary indices of MET-h · wk^{-1}	Chasan-Taber et al., 1996 (24)

TABLE 2. *Continued*

Method/Questionnaire[a]	Type of Activity[b]	Expression of Dose-Response[c,d]	Author (Reference)
Kaiser	JOB, EX, SP, LEIS, HH, CARE	5-point ordinal indices	Sternfeld et al., 1999 (84)
		4, and 5-point ordinal indices	Ainsworth et al., 2000 (9)
San Luis Valley	JOB, EX, LEIS, HH	Somewhat active (1.5 METs)	Mayer et al., 1991 (65)
		Active (4 METs)	
		Very active (6 METs)	
		Extremely active (9 METs)	
		Ordinal summary indices of kJ · kg^{-1} · wk^{-1}	
		Unitless ordinal summary scales	
Women's Determinants	JOB, EX, LEIS, HH	No leisure PA, regular PA, vigorous PA, occupational PA, housework PA, active vs inactive	Brownson et al., 2000 (21)
CAPS Typical Week	JOB, EX, SP, LEIS, TRAN HH, YRD, CARE, VOL, TOTAL	Light (<3 METs)	Ainsworth et al., 2000 (7)
		Moderate (3–6 METs)	
		Vigorous (6 METs)	
		MET-min · d^{-1}	
Quantitative history			
MN LTPA	EX, SP, LEIS, HH	Light (≤4 AMI)	Taylor et al., 1978 (85)
		Moderate (4.5–5.5 AMI)	
		Heavy (≥6 AMI)	
		AMI · d^{-1}	
MN Four-Week History	EX, LEIS, HH	Summary indices in MET-min · d^{-1}	Jacobs et al., 1993 (43)
ACLS 3-Month Recall	EX, SP, LEIS	Summary indices in MET-h · wk^{-1}	Kohl et al., 1988 (49)
		3-point ordinal scale	
Tecumseh LTPA	JOB, EX, LEIS	AMI · d^{-1}	Montoye, 1971 (67)
			Buskirk et al., 1971 (22)
Tecumseh Occupation	JOB, TRAN	Met-h · wk^{-1}	Ainsworth et al., 1993 (6)
CARDIA	JOB, EX, SP, HH	Unitless summary indices	Jacobs et al., 1989 (44)
Life in New Zealand	JOB, EX, LEIS, HH	Unitless summary indices	Hopkins et al., 1991 (41)
Yale Elderly PA	EX, LEIS, HH, CARE, YRD	Summary index in kcal · wk^{-1}	DiPietro et al., 1993 (26)
Elderly PAQ	SP, LEIS, HH	Unitless summary index	Voorrips et al., 1991 (87)
Parker LTPA	EX, SP, LEIS	Summary index in kcal · kg^{-1} · wk^{-1}	Parker et al., 1988 (72)
Historical PA	SP, LEIS	4-point ordinal scale of h · wk^{-1} and kcal · wk^{-1}	Kriska et al., 1988 (52)
Diabetes PA	JOB, EX, SP, LEIS	h · wk^{-1} and MET-h · wk^{-1}	Kriska et al., 1990 (51)
Lifetime Total	JOB, EX, SP, HH	Sedentary, light, moderate, heavy in h · wk^{-1}	Friedenreich et al., 1998 (31)

[a] CDC, Centers for Disease Control; ACSM, American College of Sports Medicine; NHIS, National Health Interview Survey; NSPHPC, National Survey of Personal Health Practices and consequences; Adventist Mortality, Seventh-day Adventists Health Study; Finnish, Kuopio Ischemic Heart Disease Risk Factor Study; NHANES I, National Health and Nutrition Examination Survey; MN Heart Health, Minnesota Heart Health Study; HIP, Health Insurance Plan of Greater New York Study of Coronary Heart Disease; NHIS/HPDP, National Health Interview Survey/Health Promotion Disease Prevention; Framingham Usual, Framingham Heart Study Usual PA; Honolulu Usual; Honolulu Heart Study Usual PA; Stanford Usual, Stanford University Center for Research in Disease Prevention Usual PA; Alameda County, Alameda County Study PA Question; Goteborg PA, Goteborg Study of Swedish Men and Women PA Question; British Usual, British Regional Heart Study Usual PA; CARDIA, Coronary Artery Risk Development in Adolescents; ARIC, Atherosclerosis Risk in Communities; LTPA, Leisure-Time Physical Activity; BRFSS, Behavioral Risk Factor Surveillance System; Kaiser, Northern California Kaiser Permanente Medical Care Program; San Luis Valley, San Luis Valley Diabetes Study; Women's Determinants, U.S. Women's Determinants Study; CAPS, Cross-Cultural Activity Participation Study; MN LTPA, Minnesota LTPA; MN Four-Week History, Minnesota Four-Week History; ACLS, Aerobics Center Longitudinal Study; Tecumseh LTPA, Tecumseh, Michigan LTPA; Parker LTPA, One-Year LTPA; Historical PA, Lifetime Physical Activity Assessment; Diabetes PA, Assessment of Physical Activity in Pima Indians; Lifetime Total, Lifetime Total Physical Activity Questionnaire.

[b] JOB, occupational; EX, exercise; SP, sport; TRAN, transportation; LEIS, leisure; HH, household; YRD, yard work; CARE, care giving; VOL, volunteer; TOTAL, total physical activity.

[c] MET, metabolic equivalent; AMI, Activity Metabolic Index; kcal, kilocalorie; kJ, kiloJoule; kg, kilogram.

[d] Qualitative units (e.g., inactive, active, light, vigorous) are presented as described by original authors, and are supplemented with the method of derivation (e.g., self-report referenced against peers, unitless summary index, MET-min · d^{-1}) when possible.

* HRR, heart rate reserve; ACSM (10) also presents intensity levels in terms of % maximal HR, %$\dot{V}O_2$ reserve, RPE, and by METs stratified on categories of age.

2) Develop an integrated physiological (e.g., HR, temperature, and ventilation) and motion (acceleration) detection system to objectively measure *movement* in free-living conditions.

3) Identify physiologic thresholds for a wide variety of PA-health relationships for use in developing evidence-based dose-response cutpoints.

4) Standardize 1) the terminology used to express EE (kcal·d^{-1}, MET-min·d^{-1}), and 2) procedures for extrapolating EE from indirect measures of PA or EE.

TABLE 3. Potential limitations to evaluating dose-response characteristics of physical activity or energy expenditure and health-related outcomes.

Lack of standardized PA constructs comprising PA questionnaires
Lack of standardized energy expenditure units (kcal, MET-min, MET-hour, hours, units)
Lack of standardized cutpoints based on physiological thresholds
Inappropriate use of ordinal scales to reflect a linear metric
Continuous vs categorical modeling
Poor understanding of the process associated with recalling PA
Duration of assessment period
Race-ethnicity effect
Sex effect
Age effect

5) Apply innovative statistical procedures for developing PA instruments and analyzing PA data (e.g., test equating or item-response theory).

6) Apply innovative statistical procedures to assess the nature of dose-response relationships (e.g., fractional polynomial regression, spline regression, and nonparametric modeling).

7) Identify sources of bias and variance in the recall of PA using questionnaires.

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Is physical activity or physical fitness more important in defining health benefits?

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ABSTRACT

BLAIR, S. N., Y. CHENG, and J. S. HOLDER. Is physical activity or physical fitness more important in defining health benefits? *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S379–S399. **Purpose:** We addressed three questions: 1) Is there a dose-response relation between physical activity and health? 2) Is there a dose-response relation between cardiorespiratory fitness and health? 3) If both activity and fitness have a dose-response relation to health, is it possible to determine which exposure is more important? **Methods:** We identified articles by PubMed search (restricted from 1/1/90 to 8/25/00) using keywords related to physical activity, physical fitness, and health. An author scanned titles and abstracts of 9831 identified articles. We included for thorough review articles that included three or more categories of activity or fitness and a health outcome and excluded articles on clinical trials, review papers, comments, letters, case reports, and nonhuman studies. We used an evidence-based approach to evaluate the quality of the published data. **Results:** We summarized results from 67 articles meeting final selection criteria. There is good consensus across studies with most showing an inverse dose-response gradient across both activity and fitness categories for morbidity from coronary heart disease (CHD), stroke, cardiovascular disease (CVD), or cancer; and for CVD, cancer, or all-cause mortality. **Conclusions:** All studies reviewed were prospective observational investigations; thus, conclusions are based on Evidence Category C. 1) There is a consistent gradient across activity groups indicating greater longevity and reduced risk of CHD, CVD, stroke, and colon cancer in more active individuals. 2) Studies are compelling in the consistency and steepness of the gradient across fitness groups. Most show a curvilinear gradient, with a steep slope at low levels of fitness and an asymptote in the upper part of the fitness distribution. 3) It is not possible to conclude whether activity or fitness is more important for health. Future studies should define more precisely the shape of the dose-response gradient across activity or fitness groups, evaluate the role of musculoskeletal fitness, and investigate additional health outcomes. **Key Words:** EPIDEMIOLOGY, MORTALITY, CARDIOVASCULAR DISEASE, CANCER, DIABETES, LONGITUDINAL STUDY

Physical activity and physical fitness are closely related in that physical fitness is mainly, although not entirely, determined by physical activity patterns over recent weeks or months. Genetic contributions to fitness are important but probably account for less of the variation observed in fitness than is due to environmental factors, principally physical activity (14). For most individuals, increases in physical activity produce increases in physical fitness, although the amount of adaptation in fitness to a standard exercise dose varies widely and is under genetic control. Thus, at one level the topic of this report reverts to the oft-considered question of the relative importance of nature versus nurture. Consensus has perhaps never been achieved in response to this nature-nurture issue in other contexts, but we will attempt to delimit and define the question addressed in this report so that many, if not most, can find some concepts or issues with which they can agree.

We considered the general case of health-related behaviors and health-related fitness as they relate to health outcomes (Fig. 1). Several examples, but not an exhaustive list, of health-related behaviors are shown on the left side of the figure. These behaviors, singly or in concert, are important determinants of the several components of health-related fitness listed in the middle of the figure. The fitness variables are important determinants of various health outcomes, and several specific biological mechanisms have been elucidated to confirm the causal relation of fitness variables to health. Just as for cardiorespiratory fitness, all of the fitness variables have genetic components but also are strongly influenced by environmental factors. For example, the blood lipid profile has a genetic component, but diet is of great importance. For most of these associations a critical issue is the genetic-environmental interactions that determine specific fitness levels. That is, a diet high in sodium may be especially important in hypertension risk in those with a genetic proclivity for salt sensitivity. Note also that for nonfatal health outcomes, there often may be a feedback loop whereby an outcome may influence one or more health behaviors.

The material presented in this review is used to address three specific questions:

1) Is there a dose-response relation between physical activity and health outcomes?

2) Is there a dose-response relation between cardiorespiratory fitness and health outcomes?

3) If both physical activity and cardiorespiratory fitness have a dose-response relation to health outcomes, is there a difference in the outcome gradient across categories for the

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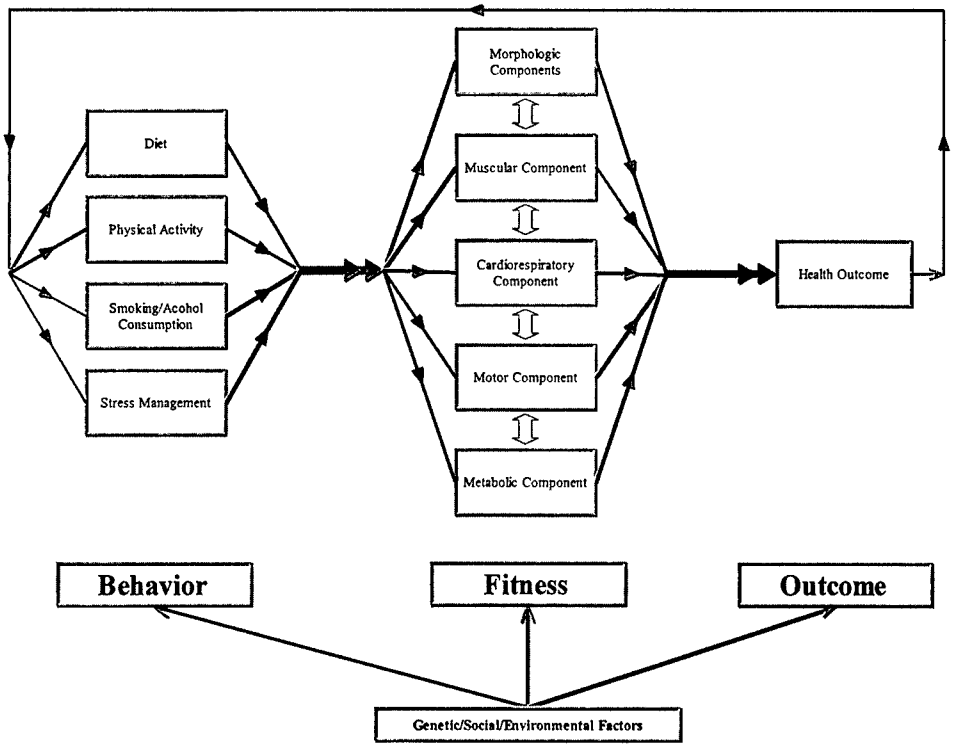


FIGURE 1—Interrelationships between health behaviors, various types of fitness, and health outcomes. Numerous health behaviors influence, singly or in concert, several different components of fitness—which in turn affect various health outcomes. Genetic, social, and environmental factors influence behaviors, fitness, and outcomes. Health outcomes can also influence behaviors.

two exposures, and is it possible to determine from the available data which exposure is more important for health?

METHODS

We first defined the exposure and outcome variables and delimited the scope of our review. We use the basic terminology presented by Howley in the introductory paper in this supplement, with some additional, more detailed specifications of some of the terms.

Exposure variables. Exposure variables for this report are physical activity and physical fitness. Physical activity in this report refers to either leisure-time physical activity or occupational activity, and we will not attempt to distinguish between these subtypes of activity. The physical fitness component addressed here is cardiorespiratory fitness, which was determined in the studies reviewed for this report by submaximal or maximal exercise tests of work performance rather than measured maximal oxygen uptake. These work performance tests, at least the maximal tests, correlate highly with measured maximal oxygen uptake (55,56).

Outcome variables. Health variables constitute the outcome variables for this report. We agree with the general definitions of health summarized by Howley, and that health is a multidimensional characteristic. Health is a diffuse and perhaps even an elusive concept and often presents a challenge to health researchers. We chose not to select various clinical measures, such as lipids, blood pressure, or body composition as outcomes, because these variables will be topics of other reports in this supplement. We also did not select one of the global definitions of health that includes physical, social, and psychological dimensions, such as those presented by Howley. These broad definitions are useful in philosophical considerations of health in broad terms, but they typically have not been used as outcome measures in research on physical activity or fitness. Therefore, we chose to examine the dose-response association of activity and fitness on major physical health outcomes, which is where there are sufficient studies. Specifically, we selected two types of health measures as the outcome variables for this report:

1) morbidity from major chronic diseases such as coronary heart disease (CHD), stroke, combined cardiovascular disease, or cancer, and

2) cardiovascular disease (CVD), cancer, or all-cause mortality.

We did not include diabetes, hypertension, or other chronic diseases as outcomes for this report. The tables,

TABLE 1. Process for identifying material included in review.

Performed PubMed computer search using keywords related to physical activity (physical activity, exercise, exertion), physical fitness (fitness, exercise tolerance, exercise test), and health outcomes (morbidity, mortality). Restricted the search from 1990 to August 25, 2000. (Because of the limited numbers of papers, search for physical fitness includes papers from the 1980s.) Computer search identified papers with at least one of the exposures (activity or fitness) and at least one of the health outcomes, and the initial search results were:

Physical activity and health	Physical fitness and health	Activity, fitness, and health
7335 papers	2706 papers	2213 papers

An author reviewed each of the papers identified above and applied selection criteria:

- Included papers with three or more levels of activity or fitness
- Excluded clinical trials, review papers, comments, letters, case reports, and non-human studies
- Selection process yielded final group of papers for thorough review

Activity and health	Fitness and health	Activity, fitness, and health
49 papers	9 papers	9 papers

TABLE 2. Physical activity and morbidity and mortality.

Study	Population/Design	Physical Activity Assessment	Adjusted for	Outcome	Summary of Results
Lee et al., 2000 (40)	N = 13,485 men Observational cohort study	Physical activity questionnaire: assessed number of blocks walked, flights of stairs climbed, and sports/recreation participation Categories in kJ·wk^{-1} for summed energy expenditure (1) <4200 (2) 4200–<8400 (3) 8400–<12,600 (4) 12,600–<16,800 (5) ≥16,800 **Categories in kJ·wk^{-1} for light, moderate, or vigorous energy activities (I) <630 (II) 630–<1680 (III) 1680–<3150 (IV) 3150–<6300 (V) ≥6300	Age, Quetelet's index, smoking, alcohol, and early parental death	All-cause mortality 2539 deaths	Adjusted RR (95% CI) Total energy expenditure (1) 1.0 (referent) (2) 0.80 (0.72–0.88) (3) 0.74 (0.65–0.83) (4) 0.80 (0.69–0.93) (5) 0.73 (0.64–0.84) Trend P < 0.001 Light activities (<4 METs) (**kJ·wk^{-1}) (I) 1.0 (referent) (II) 0.91 (0.74–1.12) (III) 0.93 (0.71–1.22) (IV) 1.07 (0.79–1.46) (V) 1.17 (0.83–1.64) Trend P = 0.72 Moderate activities (4–<6 METs) (**kJ·wk^{-1}) (I) 1.0 (referent) (II) 1.05 (0.90–1.23) (III) 0.89 (0.75–1.05) (IV) 0.82 (0.70–0.96) (V) 0.97 (0.85–1.10) Trend P = 0.07 Vigorous activities (≥6 METs) (**kJ·wk^{-1}) (I) 1.0 (referent) (II) 0.89 (0.77–1.02) (III) 0.82 (0.70–0.96) (IV) 0.82 (0.71–0.96) (V) 0.77 (0.67–0.89) Trend P = <0.001
Andersen et al., 2000 (3)	N = 11,947 women and 10,650 men (20–93 yr) Observational cohort study	Self-reported physical activity Categories of leisure-time physical activity: 1 (sedentary) to 3 + 4 (most active) Levels 3 + 4 were analyzed together since the number of subjects and deaths in the most physically active in leisure time was limited	Age, systolic blood pressure, smoking, and other risk factors	All-cause mortality Men: 3259 deaths Women: 2458 deaths	Adjusted RR (95% CI) Men (1) 1.0 (referent) (2) 0.72 (0.66–0.78) (3 + 4) 0.71 (0.65–0.78) Women (1) 1.0 (referent) (2) 0.65 (0.60–0.71) (3 + 4) 0.59 (0.52–0.67)
Bijnen et al., 1999 (8)	N = 472 elderly Dutch men Observational cohort study Surveys taken in 1985 and 1990	Self-reported physical activity Categories based on tertiles of time spent on physical activity: (1) Low (2) Middle (3) High	Age, disease, functional status, and lifestyle factors adjusted in 1990	All-cause mortality 118 deaths	Adjusted RR (95% CI) All-cause (based on 1985 survey) (1) 1.0 (referent) (2) 1.25 (0.79–1.99) (3) 1.25 (0.73–2.12) Trend P = 0.39 All-cause (based on 1990 survey) (1) 1.0 (referent) (2) 0.56 (0.35–0.89) (3) 0.44 (0.25–0.80) Trend P < 0.01
Wannamethee et al., 1998 (72)	N = 4311 men Observational cohort study	Self-reported physical activity questionnaires in 1978–80 or 1992 measuring regular walking or cycling, recreational activity, or vigorous sports activity Categories of physical activity: (1) Inactive or occasionally active (2) Light (3) Moderate (4) Moderately vigorous/vigorous	Age, smoking, social class, body-mass index, and self-perception of health	All-cause and CVD mortality 219 deaths 93 CVD deaths	Adjusted RR (95% CI) All-cause (1) 1.0 (referent) (2) 0.61 (0.43–0.86) (3) 0.50 (0.31–0.79) (4) 0.65 (0.45–0.94) CVD (1) 1.0 (referent) (2) 0.61 (0.36–1.04) (3) 0.36 (0.16–0.80) (4) 0.65 (0.37–1.14)
Weller and Corey, 1998 (73)	N = 6620 Canadian women > 30 yr of age Observational cohort study	Self-reported leisure and nonleisure time physical activities Categories of physical activity 1 (lowest) to 4 (highest)	Age	CVD and all-cause mortality 449 deaths 159 CVD deaths	Adjusted RR (95% CI) All-cause (1) RR = 1.0 (2) 0.86 (0.66–1.13) (3) 0.68 (0.51–0.91) (4) 0.73 (0.54–1.00) Trend P = 0.03 CVD (1) 1.0 (referent) (2) 1.01 (0.68–1.51) (3) 0.70 (0.44–1.11) (4) 0.51 (0.28–0.91) Trend P = 0.01

TABLE 2. *Continued*

Study	Population/Design	Physical Activity Assessment	Adjusted for	Outcome	Summary of Results
Bijnen et al., 1998 (7)	*N* = 802 Dutch men (64 to 84 yr at baseline) Observational cohort study	Self-reported physical activity Categories based on tertiles of time spent on physical activity (1) Low (2) Middle (3) High	Age, disease, and lifestyle factors	CVD, stroke, and all-cause mortality 373 deaths 199 CVD deaths 47 stroke deaths	Adjusted RR (95% CI) All-cause (1) 1.0 (referent) (2) 0.80 (0.63–1.02) (3) 0.77 (0.59–1.00) Trend $P = 0.04$ CVD (1) 1.0 (referent) (2) 0.75 (0.54–1.04) (3) 0.70 (0.48–1.01) Trend $P = 0.04$ Stroke (1) 1.0 (referent) (2) 0.65 (0.33–1.25) (3) 0.55 (0.24–1.26) Trend $P = 0.12$
Kujala et al., 1998 (34)	*N* = 7925 healthy men, and 7977 healthy women (25–64 yr) Observational twin cohort study	Self-reported leisure time physical activity Categories of leisure time physical activity (1) Sedentary (2) Occasional exercisers (3) Conditioned exercisers	Age and sex	All-cause mortality 1253 deaths Men: 829 Women: 424	Adjusted RR (95% CI) Overall all-cause mortality (1) 1.0 (referent) (2) 0.71 (0.62–0.81) (3) 0.57 (0.45–0.74) Trend $P < 0.001$ Twins healthy at baseline and discordant for death (1) 1.0 (referent) (2) 0.66 (0.46–0.94) (3) 0.44 (0.23–0.83) Trend $P = 0.005$
Kushi et al., 1997 (35)	*N* = 40,417 postmenopausal Iowa women (55–69 yr at baseline) Observational cohort study with 7 yr of follow-up	Self-reported physical activity Categories of physical activity include (1) Low (2) Medium (3) High	Age and other risk factors	All-cause mortality 2260 deaths	Adjusted RR (95% CI) Age-adjusted (1) 1.0 (referent) (2) 0.66 (0.60–0.73) (3) 0.58 (0.52–0.65) Trend $P < 0.001$ Multivariate-adjusted (1) 1.0 (referent) (2) 0.77 (0.69–0.86) (3) 0.68 (0.60–0.77) Trend $P < 0.001$
Morgan and Clark, 1997 (49)	*N* = 635 women and 406 men ≥65 yr Observational cohort study	Self-reported customary physical activity: outdoor productive activities, indoor productive activities, walking, shopping, and leisure time activities Categories of physical activity (1) Low (2) Middle (3) High		All-cause mortality Men: 247 deaths Women: 321 deaths	Adjusted RR (95% CI) Men (1) 1.59 (1.12–2.29) (2) 1.35 (0.96–1.89) (3) 1.0 (referent) Women (1) 2.07 (1.53–2.79) (2) 1.53 (1.12–2.09) (3) 1.0 (referent)
Folsom et al., 1997 (21)	*N* = 7852 biracial women and 6188 biracial men 45–64 yr Multicenter observational cohort study	Physical activity questionnaire Categories of physical activity are represented as quartiles (Q1 = low to Q4 = high) determined by index score on the questionnaire	Age, race, smoking, systolic blood pressure, education level, field center, and other risk factors	CHD incidence and all-cause mortality Men: 260 deaths and 223 CHD cases Women: 181 deaths and 97 CHD cases	Adjusted RR (95% CI) All-cause mortality Men Q1 1.0 (referent) Q2 0.81 (0.59–1.11) Q3 0.85 (0.57–1.26) Q4 0.63 (0.44–0.91) Trend $P = 0.02$ Women Q1 1.0 (referent) Q2 0.79 (0.54–1.17) Q3 1.05 (0.68–1.64) Q4 0.55 (0.35–0.86) Trend $P = 0.04$ CHD Incidence Men Q1 1.0 (referent) Q2 0.96 (0.67–1.37) Q3 0.70 (0.44–1.13) Q4 0.76 (0.51–1.13) Trend $P = 0.08$ Women Q1 1.0 (referent) Q2 0.74 (0.43–1.27) Q3 0.85 (0.44–1.64) Q4 0.56 (0.30–1.06) Trend $P = 0.12$

TABLE 2. *Continued*

Study	Population/Design	Physical Activity Assessment	Adjusted for	Outcome	Summary of Results
Haapanen et al., 1997 (25)	N = 842 men and 953 women 35–63 yr Observational cohort study	Self-reported leisure time physical activity Categories of physical activity based on index score from physical activity questionnaire (1) Low (2) Moderate (3) High	Age, smoking	CHD incidence Men: 108 cases Women: 75 cases	Adjusted RR (95% CI) CHD incidence Men (1) 1.98 (1.22–3.23) (2) 1.33 (0.78–2.27) (3) 1.0 (referent) Trend P = 0.014 Women (1) 1.25 (0.72–2.15) (2) 0.73 (0.38–1.39) (3) 1.0 (referent) Trend P = 0.178
Mensink et al., 1996 (48)	N = 7689 men and 7747 women 25–69 yr Observational cohort study	Self-reported leisure time physical activity Categories of physical activity (1) Low (2) Moderate (3) High	Age, BMI, smoking, systolic blood pressure, and other risk factors	All-cause and CVD mortality Men: 67 deaths 34 CVD deaths Women: 48 deaths 17 CVD deaths	Adjusted RR (95% CI) All-cause Men (1) 1.0 (referent) (2) 0.56 (0.30–1.04) (3) 0.78 (0.42–1.44) Women (1) 1.0 (referent) (2) 1.24 (0.60–258) (3) 1.29 (0.58–2.85) CVD Men (1) 1.0 (referent) (2) 0.38 (0.15–0.97) (3) 0.80 (0.34–1.85) Women (1) 1.0 (referent) (2) 3.20 (0.68–15.07) (3) 2.83 (0.54–14.80)
Kaplan et al., 1996 (32)	N = 6131 men and women Observational cohort study	Self-reported leisure time physical activity Physical activity categories divided into tertiles 1-Low activity 2-Moderate activity 3-High activity		All-cause and CVD mortality Men: 639 deaths 321 CVD deaths Women: 587 deaths 388 CVD deaths	All-cause Men Crude death rate/1000 py Tertile 1 24.68 Tertile 2 11.37 Tertile 3 7.59 Women Crude death rate/1000 py Tertile 1 18.03 Tertile 2 7.66 Tertile 3 3.88 CVD Men Crude death rate/1000 py Tertile 1 13.13 Tertile 2 5.87 Tertile 3 2.98 Women Crude death rate/1000 py Tertile 1 15.11 Tertile 2 3.46 Tertile 3 1.14
Haapanen et al., 1996 (24)	N = 1072 men Observational cohort study	Self-reported leisure time physical activity Categories of physical activity based on estimated energy expenditure (kcal·wk^{-1}) (1) 0–800 (2) 800.1–1500 (3) 1500.1–2100 (4) >2100	Age, disease, and other risk factors	All-cause and CVD mortality 168 deaths 93 CVD deaths	Adjusted RR (95% CI) All-cause (1) 2.74 (1.46–5.14) (2) 1.10 (0.55–2.21) (3) 1.74 (0.87–3.50) (4) 1.0 (referent) Trend P < 0.001 CVD (1) 3.58 (1.45–8.85) (2) 0.99 (0.34–2.87) (3) 1.59 (0.56–4.49) (4) 1.0 (referent) Trend P < 0.001
Lee et al., 1995 (38)	N = 17,321 men Observational cohort study from 1962 to 1988	Self-reported physical activity on a mail-back questionnaire Physical activity divided into vigorous (requiring ≥ 6 METs) or nonvigorous (requiring < 6 METs) Physical activity levels further divided based on estimated energy expenditure (kJ·wk^{-1}) (1) <630 (2) 630 < 1680 (3) 1680 < 3150 (4) 3150 < 6300 (5) ≥ 6300	Age, smoking, and other risk factors	All-cause mortality 3728 deaths	Adjusted RR (95% CI) Vigorous activities (1) 1.0 (referent) (2) 0.88 (0.82–0.96) (3) 0.92 (0.82–1.02) (4) 0.87 (0.77–0.99) (5) 0.87 (0.78–0.97) Trend P = 0.007 Nonvigorous activities (1) 1.0 (referent) (2) 0.89 (0.79–1.01) (3) 1.00 (0.89–1.12) (4) 0.98 (0.88–1.12) (5) 0.92 (0.82–1.02) Trend P = 0.36

TABLE 2. *Continued*

Study	Population/Design	Physical Activity Assessment	Adjusted for	Outcome	Summary of Results
Rodriguez et al., 1994 (58)	*N* = 7074 Japanese-American men Observational cohort study	Self-reported physical activity Physical activity levels in tertiles (1) Low (2) Middle (3) High	Age, smoking, and other risk factors	CHD incidence and mortality 340 CHD deaths 789 CHD cases	Adjusted RR (95% CI) CHD mortality (1) 1.0 (referent) (2) 1.19 (0.93–1.53) (3) 0.85 (0.65–1.13) CHD incidence (1) 1.0 (referent) (2) 1.07 (0.90–1.26) (3) 0.95 (0.80–1.14)
Shaper and Wannamethee, 1991 (61)	*N* = 5714 men 40–59 yr without prior IHD Observational cohort study	Self-reported physical activity Scores based on frequency, type, and intensity of physical activity divided in the following categories (1) Inactive (2) Occasional (3) Light (4) Moderate (5) Moderately vigorous (6) Vigorous	Age, body mass index, social class, and smoking status **adjusted for additional risk factors (SBP, total cholesterol, HDL cholesterol, breathlessness, FEV, and heart rate)	Ischemic heart disease 488 cases of ischemic heart disease	Adjusted RR (95% CI) (1) 1.0 (referent) (2) 0.80 (0.50–1.20) (3) 0.80 (0.50–1.20) (4) 0.40 (0.20–0.80) (5) 0.40 (0.20–0.80) (6) 0.80 (0.40–1.40) **Adjusted for additional risk factors (1) 1.0 (referent) (2) 0.90 (0.50–1.30) (3) 0.90 (0.60–1.40) (4) 0.50 (0.20–0.80) (5) 0.50 (0.30–0.90) (6) 0.90 (0.50–1.80)
Lindsted et al., 1991 (46)	*N* = 9484 Seventh-day Adventist men Observational cohort study from 1960 to 1985	Self-reported physical activity Physical activity levels (1) Low (2) Moderate (3) High	Race, smoking, education, BMI, medical illness, marital status, and dietary pattern	All-cause CVD, and cancer mortality 3799 deaths 2137 CVD deaths 655 cancer deaths	Adjusted RR (95% CI) All-cause Age 50 (1) 1.0 (referent) (2) 0.61 (0.50–0.74) (3) 0.66 (0.50–0.87) 60 (1) 1.0 (referent) (2) 0.68 (0.59–0.78) (3) 0.76 (0.63–0.92) 70 (1) 1.0 (referent) (2) 0.76 (0.69–0.83) (3) 0.89 (0.78–1.01) 80 (1) 1.0 (referent) (2) 0.85 (0.78–0.92) (3) 1.03 (0.91–1.16) 90 (1) 1.0 (referent) (2) 0.94 (0.84–1.06) (3) 1.19 (0.99–1.43) CVD Age 50 (1) 1.0 (referent) (2) 0.57 (0.42–0.77) (3) 0.68 (0.45–1.02) 60 (1) 1.0 (referent) (2) 0.65 (0.53–0.81) (3) 0.78 (0.59–1.04) 70 (1) 1.0 (referent) (2) 0.75 (0.65–0.86) (3) 0.90 (0.75–1.07) 80 (1) 1.0 (referent) (2) 0.86 (0.77–0.96) (3) 1.03 (0.88–1.21) 90 (1) 1.0 (referent) (2) 0.98 (0.84–1.15) (3) 1.18 (0.93–1.51) Cancer Age 50 (1) 1.0 (referent) (2) 0.65 (0.42–1.01) (3) 0.75 (0.42–1.30) 60 (1) 1.0 (referent) (2) 0.78 (0.58–1.06) (3) 0.93 (0.63–1.35) 70 (1) 1.0 (referent) (2) 0.94 (0.76–1.17) (3) 1.15 (0.88–1.52) 80 (1) 1.0 (referent) (2) 1.13 (0.89–1.44) (3) 1.43 (1.02–2.00) 90 (1) 1.0 (referent) (2) 1.36 (0.95–1.95) (3) 1.78 (1.08–2.95)

TABLE 2. *Continued*

Study	Population/Design	Physical Activity Assessment	Adjusted for	Outcome	Summary of Results
Morris et al., 1990 (50)	*N* = 9376 male civil servants Observational cohort study	Self-reported leisure time physical activity Group 4 (no vigorous aerobic activity) to Group 1 (much vigorous aerobic activity)	Age, smoking, family history, stature, BMI, and "subclinical" CVD	CHD mortality 109 CHD deaths in ages 45–54 178 CHD deaths in ages 55–64	Adjusted RR (95% CI) Ages 45–54 Group 4 1.0 (referent) Group 3 1.41 (0.83–2.40) Group 2 1.98 (1.03–3.78) Group 1 0.25 (0.07–0.93) Ages 55–64 Group 4 1.0 (referent) Group 3 0.90 (0.57–1.44) Group 2 0.59 (0.34–1.05) Group 1 0.53 (0.21–1.32)
Physical activity and cancer					
Verloop et al., 2000 (70)	*N* = 1836 women Case-control study	Self-reported activities at age 10–12 yr and 13–15 yr, lifetime recreational activity, and title of longest held job Compare total physical activity at ages 10–12 yr and 13–15 yr with activity of their peers (1) less active (2) equally active (3) more active Lifetime physical activities (I) not active (II) moderate active: all recreational activity other than extreme activities (III) extreme active: more than 2 times/wk, duration > 11 yr, intensity > 5.5 MET score	Age, region, education, family history, benign breast disease, smoking habit, parity, parous, alcohol consumption, age at menarche, menstrual complaints, premenstrual complaints, BMI	Breast cancer morbidity 918 cases	Adjusted OR (95% CI) Activity compared with that of peer group at age 10–12 yr (1) 1.0 (referent) (2) 0.82 (0.61–1.09) (3) 0.68 (0.49–0.94) Activity compared with that of peer group at age 13–15 yr (1) 1.0 (referent) (2) 0.81 (0.61–1.07) (3) 0.77 (0.57–1.05) Lifetime recreational activities (I) 1.0 (referent) (II) 0.70 (0.56–0.89) (III) 0.60 (0.38–0.93)
Srivastava et al., 2000 (64)	*N* = 463 men Case-control study	Self-reported recreational and occupational physical activity. Moderate and strenuous levels not explicitly defined, but examples of activities such as "gardening" or "brisk walking" given for moderate activity; for strenuous activity, a minimum period of 20 min was specified Levels of recreational physical activity (1) < once/month (2) 1–3 times/month (3) 1–2 times/week (4) 3–5 times/week (5) >5 times/week Levels of occupational activity (1) Sitting (2) Light (3) Moderate (4) Strenuous	Age, BMI, marital status, education, smoking, vegetable consumption, fruit consumption	Testicular cancer morbidity 212 cases	Adjusted OR (95% CI) Recreational physical activity 2 previous yr Moderate: (1) 1.0 (referent); (2) 1.68 (0.70–4.04); (3) 1.06 (0.48–2.34); (4) 1.42 (0.64–3.17); (5) 1.41 (0.61–3.29) Strenuous: 1.0 (referent); 1.50 (0.77–2.90); 1.19 (0.64–2.23); 1.09 (0.57–2.09); 1.18 (0.52–2.65) Activity in teenage years Moderate: (1) 1.0 (referent); (2) combine (3); (3) 1.15 (0.54–2.44); (4) 1.77 (0.88–3.53); (5) 2.36 (1.20–4.64) Strenuous: 1.0 (referent); 1.94 (0.66–5.74); 2.04 (0.83–5.04); 2.07 (0.91–4.72); 2.58 (1.14–5.85) Activity in early 30s Moderate: (1) 1.0 (referent); (2) 1.13 (0.44–2.89); (3) 1.22 (0.51–2.91); (4) 1.34 (0.56–3.22); (5) 1.74 (0.68–4.42) Strenuous: 1.0 (referent); 1.37 (0.67–2.79); 1.20 (0.60–2.37); 1.21 (0.58–2.53); 1.27 (0.52–3.10) Occupational physical activity 2 previous yr (1) 1.0 (referent) (2) 1.32 (0.73–2.37) (3) 0.98 (0.55–1.75) (4) 0.94 (0.46–1.90) Activity in early 20s (1) 1.0 (referent) (2) 1.30 (0.71–2.39) (3) 1.85 (1.05–3.26) (4) 1.67 (0.92–3.00) Activity in early 30s (1) 1.0 (referent) (2) 0.99 (0.51–1.94) (3) 1.46 (0.77–2.78) (4) 1.30 (0.60–2.78)

TABLE 2. *Continued*

Study	Population/Design	Physical Activity Assessment	Adjusted for	Outcome	Summary of Results
Rockhill et al., 1999 (57)	N = 121,701 women Observational cohort study	Self-reported recreational physical activity Activity level (h·wk^{-1}) (1) <1 (2) 1.0–1.9 (3) 2.0–3.9 (4) 4.0–6.9 (5) ≥7	Age, BMI, age at menarche, benign breast disease, family history, parity, age at first birth, menopausal status, postmenopausal hormone use	Breast cancer morbidity and mortality 3137 cases	Adjusted RR (95% CI) Cumulative measurement averages / Baseline (1980 only) (one-time) (1) 1.0 (referent) / 1.0 (referent) (2) 0.88 (0.79–0.98) / 1.03 (0.90–1.17) (3) 0.89 (0.81–0.99) / 0.97 (0.88–1.07) (4) 0.85 (0.77–0.94) / 0.90 (0.80–1.01) (5) 0.82 (0.70–0.97) / 0.89 (0.80–0.98) Trend P = 0.004 / P = 0.004
Bergstrom et al., 1999 (5)	N = 674,025 men and 253,336 women Observational cohort study	Self-reported occupational physical activity Physical activities divided into 4 groups according to occupational code (1) Sedentary (2) Light (3) Medium (4) Very high/high	Age, socioeconomic status, place of residence, calendar year of follow-up	Renal cell cancer morbidity Men: 2704 cases Women: 587 cases	Adjusted RR (95% CI) Men / Women (1) 1.25 (1.02–1.53) / 0.80 (0.51–1.27) (2) 1.16 (0.99–1.36) / 1.01 (0.76–1.35) (3) 1.11 (0.97–1.27) / 0.99 (0.77–1.29) (4) 1.0 (referent) / 1.0 (referent) Trend P = 0.03 / P > 0.50
Lee et al., 1999 (43)	N = 13,905 men Observational cohort study	Self-reported physical activity Total energy expenditure at baseline physical activity levels (kJ·wk^{-1}): (1) <4200 (2) 4200–8399 (3) 8400–12,599 (4) ≥12,600 For sports or recreational activities, energy expenditure from light (<4.5 METs) and at least moderate intensity (≥4.5 METs) activities physical activity levels (kJ·wk^{-1}) (I) none (II) 1–1049 (III) 1050–2519 (IV) 2520–5879 (V) ≥5880	Age, smoking habit, BMI	Lung cancer morbidity and mortality 245 cases	Adjusted RR (95% CI) Total physical activities (1) 1.0 (referent) (2) 0.87 (0.64–1.18) (3) 0.76 (0.52–1.11) (4) 0.61 (0.41–0.89) Trend test: P = 0.008 <4.5 METs / ≥4.5 METs (I) 1.0 (referent) / 1.0 (referent) (II) 1.20 (0.79–1.83) / 0.84 (0.58–1.22) (III) 0.92 (0.57–1.48) / 0.64 (0.39–1.04) (IV) 0.81 (0.50–1.32) / 0.93 (0.62–1.39) (V) 0.99 (0.66–1.48) / 0.60 (0.38–0.96) Trend P = 0.62 / P = 0.046
Tang et al., 1999 (66)	N = 179 men and 137 women Case-control study	Self-reported leisure time physical activity The MET scoring system for physical activity level (1) Sedentary, 0 MET h·wk^{-1} (2) Moderate, 1–<20 MET h·wk^{-1} (3) Active, ≥20 MET h·wk^{-1}	Age, smoking habits, water intake, alcohol consumption, dietary habit	Colon or rectal cancer morbidity Men: 92 cases Women: 71 cases	Adjusted OR (95% CI) Colon cancer Men / Women (1) 1.0 (referent) / 1.0 (referent) (2) 2.22 (0.68–7.21) / 0.52 (0.13–2.03) (3) 0.19 (0.05–0.77) / 0.63 (0.18–2.18) Trend P = 0.03 / P = 0.48 Rectal cancer Men / Women (1) 1.0 (referent) / 1.0 (referent) (2) 1.48 (0.43–5.09) / 1.21 (0.42–3.46) (3) 0.44 (0.13–1.49) / 0.84 (0.28–2.46) Trend P = 0.24 / P = 0.74
Martinez et al., 1997 (47)	N = 89,448 women Observational cohort study	Self-reported recreational physical activity MET-h·wk^{-1} score (1) <2 (2) 2–4 (3) 4–10 (4) 11–21 (5) >21	Age, smoking history, family history, BMI, postmenopausal hormone use, aspirin use, intake of red meat, alcohol consumption	Colon cancer morbidity and mortality 396 cases	Adjusted RR (95% CI) (1) 1.0 (referent) (2) 0.71 (0.44–1.15) (3) 0.78 (0.50–1.20) (3) 0.67 (0.42–1.07) (4) 0.54 (0.33–0.90) Trend P = 0.03
Thune et al., 1997 (68)	N = 53,242 men and 28,274 women Observational cohort study	Self-reported occupational and recreational physical activity Occupational physical activities were categorized as (1) Mostly sedentary work (2) Work with much walking (3) Work with much lifting and walking (4) Heavy manual work Recreational activities categorized as (I) Reading, watching TV, or other sedentary activities (II) Walking, bicycling, or physical activities for at least 4 h·wk^{-1} (III) Exercise to keep fit, participating in recreational athletics, etc., for at least 4 h·wk^{-1}, regular hard training, or participation in competitive sports several times a week	Age, geographical region, smoking habits, BMI	Lung cancer morbidity Men: 402 cases Women: 51 cases	Adjusted RR (95% CI) Occupational physical activity Men / Women (1) 1.0 (referent) / 1.0 (referent) (2) 1.15 (0.90–1.47) / 0.81 (0.37–1.76) (3) 1.13 (0.87–1.47) / 0.79 (0.30–2.12) (4) 0.99 (0.70–1.41) / — Trend P = 0.71 / P = 0.30 Recreational physical activity Men / Women (I) 1.0 (referent) / 1.0 (referent) (II) 0.75 (0.60–0.94) / 0.91 (0.48–1.71) (III) 0.71 (0.52–0.97) / 0.99 (0.35–2.78) Trend P = 0.01 / P = 0.88

TABLE 2. *Continued*

Study	Population/Design	Physical Activity Assessment	Adjusted for	Outcome	Summary of Results
Thune et al., 1996 (67)	N = 53,242 men and 28,274 women Observational cohort study	Self-reported occupational and recreational physical activity Same scales for recreational and occupational activities as above reference Total physical activity levels (combined recreational and occupational) (1) Sedentary: R1+O1–2 (2) Moderate: R1+O3–4, O1+R3–4 (3) Active: O2–4+R2–4.	Age, BMI, serum cholesterol, and geographic region	Colon or rectal cancer morbidity Men: 496 cases Women: 153 cases	Adjusted RR (95% CI) Colon cancer and total physical activity Men / Women (1) 1.0 (referent) / 1.0 (referent) (2) 1.18 (0.76–1.82) / 0.97 (0.33–2.77) (3) 0.97 (0.63–1.50) / 0.63 (0.39–1.04) Trend P = 0.49 / P = 0.04 Rectal cancer and total physical activity Men / Women (1) 1.0 (referent) / 1.0 (referent) (2) 1.24 (0.73–2.08) / 0.96 (0.33–2.77) (3) 1.20 (0.72–2.02) / 1.27 (0.59–2.72) Trend P = 0.63 / P = 0.45
White et al., 1996 (74)	N = 484 men and 387 women Case-control study	Self-reported recreational and occupational activities Total recreational physical activity (episodes/week) (1) 0 (2) <1 (3) 1–<2 (4) 2–<4 (5) ≥4 Total occupational physical activity ($h \cdot wk^{-1}$) Men / Women (I) <10 / 0 (II) 10.0–<20.0 / <13.5 (III) 20–<35.0 / ≥13.5 (IV) ≥35	Age	Colon cancer morbidity Men: 251 cases Women: 193 cases	Adjusted RR (95% CI) Total recreational physical activity Men / Women (1) 1.0 (referent) / 1.0 (referent) (2) 0.81 (0.45–1.44) / 0.94 (0.60–1.47) (3) 0.53 (0.30–0.94) / 0.77 (0.50–1.19) (4) 0.57 (0.33–1.00) / 0.57 (0.39–0.85) (5) 0.67 (0.40–1.11) / 0.83 (0.57–1.22) Trend P = 0.03 / P = 0.04 Total occupational physical activity Men / Women (I) 1.0 (referent) / 1.0 (referent) (II) 1.03 (0.61–1.75) / 1.26 (0.76–2.07) (III) 1.04 (0.63–1.71) / 1.00 (0.60–1.65) (IV) 0.86 (0.52–1.42) / — Trend P = 0.57 / P = 0.97
Bernstein et al., 1994 (6)	N = 1090 women Case-control study	Self-reported physical activities Physical activity levels ($h \cdot wk^{-1}$) (1) none (2) 0.1–0.7 (3) 0.8–1.6 (4) 1.7–3.7 (5) ≥3.8	Age at menarche, age at first full-term pregnancy, number of full-term pregnancies, months of lactation, family history, Quetelet's index at reference date, total months of oral contraceptive use up to the reference date	Breast cancer morbidity 545 cases	Adjusted OR (95% CI) Overall activity (1) 1.0 (referent) (2) 0.95 (0.64–1.41) (3) 0.65 (0.45–0.96) (4) 0.80 (0.54–1.17) (5) 0.42 (0.27–0.64) Trend P = 0.0001 Activity within 10 years after menarche (1) 1.0 (referent) (2) 0.93 (0.63–1.38) (3) 0.78 (0.52–1.19) (4) 0.69 (0.45–1.05) (5) 0.70 (0.47–1.06) Trend P = 0.027
Dorgan et al., 1994 (15)	N = 2307 women Observational cohort study	Self-reported physical activity Physical activity index Sleep and rest = 1.0 Sedentary = 1.1 Slight = 1.5 Moderate = 2.4 Heavy = 5.0 Physical activity levels: 1–4 quartiles from lowest to highest	Age, age at first pregnancy, education, occupation, alcohol consumption	Breast cancer morbidity 117 cases	Adjusted RR (95% CI) Physical activity index by quartile (1) 1.0 (referent) (2) 1.2 (0.7–2.1) (3) 1.3 (0.7–2.4) (4) 1.6 (0.9–2.9)
Sturgeon et al., 1993 (65)	N = 702 women Case-control study	Self-reported physical activity (1) Inactive (2) Average (3) Active	Age, study area, education, parity, years use of oral contraceptives, years use of menopausal estrogens, smoking habits, BMI	Endometrial cancer morbidity 405 cases	Adjusted OR (95% CI) Recreational / Nonrecreational (1) 1.2 (0.7–2.0) / 2.0 (1.2–3.1) (2) 1.0 (0.6–1.5) / 1.2 (0.8–2.0) (3) 1.0 (referent) / 1.0 (referent)
Levi et al., 1993 (44)	N = 846 women Case-control study	Self-reported physical activity (1) Very low (2) Moderately low (3) Moderately high (4) High	Age, study center, education, parity, menopausal status, use of oral contraceptives and estrogen replacement treatment, BMI, estimated total calorie intake	Endometrial cancer morbidity 274 cases	Adjusted OR (95% CI) Sports and leisure activity (1) 1.9 (0.9–4.0) (2) 1.0 (0.5–2.3) (3) 1.0 (0.5–2.4) (4) 1.0 (referent) Trend P < 0.01 Occupational activity (1) 1.5 (1.0–2.2) (2) 1.0 (0.5–2.2) (3) 1.1 (0.5–2.3) (4) 1.0 (referent) Trend P < 0.05

TABLE 2. *Continued*

Study	Population/Design	Physical Activity Assessment	Adjusted for	Outcome	Summary of Results
Shu et al., 1993 (62)	*N* = 536 women Case-control study	Self-reported occupational and recreational physical activities Physical activity levels (kcal·d^{-1}) (1) ≤1833 (2) 1833–2126 (3) 2126–2463 (4) ≥2463	Age	Endometrial cancer morbidity 268 cases	Adjusted RR (95% CI) (1) 1.0 (referent) (2) 1.2 (0.7–2.1) (3) 1.2 (0.7–2.0) (4) 2.3 (1.4–3.7)
Lee et al., 1992 (42)	*N* = 17,719 men Observational cohort study	Self-reported physical activity Tertiles of energy expenditure (kcal·wk^{-1}) (1) Inactive (<1000) (2) Moderately active (1000–2500) (3) Highly active (>2500)	Age	Prostatic cancer morbidity and mortality 221 cases	Adjusted RR (95% CI) (1) 1.0 (referent) (2) 0.97 (0.77–1.21) (3) 0.99 (0.78–1.26) Trend *P* = 0.94
Lee et al., 1991 (41)	*N* = 17,148 men Observational cohort study	Self-reported physical activity Physical activity levels (kcal·wk^{-1}) (1) Inactive (<1000) (2) Moderately active (1000–2500) (3) Highly active (>2500)	Age	Colorectal cancer morbidity and mortality 269 cases	Adjusted RR (95% CI) Colon cancer / Rectal cancer (1) 1.0 (referent) / 1.0 (referent) (2) 0.88 (0.68–1.14) / 1.01 (0.54–1.89) (3) 0.85 (0.64–1.12) / 1.43 (0.78–2.60) Trend *P* = 0.31 / *P* = 0.34
De Verdier et al., 1990 (22)	*N* = 720 men and women Case-control study	Self-reported physical activity Physical activity levels (1) Sedentary during both working and recreational hours (2) All others than 1 and 3 (3) Very active during working and/or recreational hours	Year of birth, gender, BMI, intake of total energy, total fat, fiber, browned meat surface	Colon and rectal cancer morbidity Men: 270 cases Women: 299 cases	Adjusted OR (95% CI) Colon cancer / Right colon cancer (1) 1.8 (1.0–3.4) / 1.0 (0.4–2.4) (2) 1.4 (0.9–2.2) / 1.3 (0.7–2.2) (3) 1.0 (referent) / 1.0 (referent) Left colon cancer / Rectal cancer (1) 3.1 (1.4–7.0) / 0.9 (0.4–1.8) (2) 1.4 (0.7–2.7) / 0.8 (0.5–1.2) (3) 1.0 (referent) / 1.0 (referent)
Physical activity and stroke					
Hu et al., 2000 (29)	*N* = 72,488 women Observational cohort study	Self-reported recreational physical activity Physical activity levels (h·wk^{-1}) (1) 0–2.0 (2) 2.1–4.6 (3) 4.7–10.4 (4) 10.5–21.7 (5) >21.7	Age, follow-up time, smoking habit, BMI, menopausal status, postmenopausal and hormone replacement therapy history, family history, aspirin use, history of hypertension, diabetes, hypercholesterolemia	Ischemic stroke, hemorrhagic stroke morbidity and mortality 407 cases	Adjusted RR (95% CI) Ischemic stroke / Hemorrhagic stroke (1) 1.0 (referent) / 1.0 (referent) (2) 0.87 (0.62–1.23) / 0.92 (0.53–1.61) (3) 0.83 (0.58–1.19) / 0.89 (0.50–1.59) (4) 0.76 (0.52–1.11) / 0.69 (0.36–1.32) (5) 0.52 (0.33–0.80) / 1.02 (0.58–1.82) Trend *P* = 0.003 / *P* = 0.88
Ellekjaer et al., 2000 (17)	*N* = 14,101 women Observational cohort study	Self-reported recreational physical activity (1) Low (2) Medium (3) High	Age, smoking status, diabetes, BMI, antihypertensive medication, systolic blood pressure, angina pectoris, myocardial infarction, illness that impairs function, education	Stroke mortality 457 deaths	Adjusted RR (95% CI) (1) 1.0 (referent) (2) 0.77 (0.61–0.98) (3) 0.52 (0.38–0.72) Trend *P* < 0.0001
Lee et al., 1999 (37)	*N* = 21,823 men Observational cohort study	Self-reported recreational physical activities Physical activity levels (times/wk) (1) <1 (2) 1 (3) 2–4 (4) ≥5	Age, smoking habit, alcohol consumption, angina, family history, BMI, hypertension, high cholesterol, diabetes	Ischemic stroke, hemorrhagic stroke morbidity and mortality 533 cases	Adjusted RR (95% CI) Ischemic stroke / Hemorrhagic stroke (1) 1.0 (referent) / 1.0 (referent) (2) 0.90 (0.66–1.22) / 0.54 (0.25–1.13) (3) 0.95 (0.74–1.22) / 0.71 (0.41–1.23) (4) 0.97 (0.71–1.32) / 0.54 (0.26–1.15) Trend *P* = 0.81 / *P* = 0.10
Evenson et al., 1999 (19)	*N* = 6279 men and 8296 women Observational cohort study	Self-reported sport, leisure, and work physical activity Baecke score	Age, race-center, sex, education, smoking, hypertension, fibrinogen, BMI, diabetes	Ischemic stroke morbidity and mortality Men: 93 cases Women: 86 cases	Adjusted RR (95% CI) of incident ischemic stroke per 1-unit increase in Baecke score Sport: 1.03 (0.83–1.26) Leisure: 0.99 (0.75–1.29) Work: 0.94 (0.81–1.10)
Lee et al., 1998 (39)	*N* = 11,130 men Observational cohort study	Self-reported physical activity Physical activity levels (kcal/week) (1) <1000 (2) 1000–1999 (3) 2000–2999 (4) 3000–3999 (5) >3999	Age, smoking, alcohol consumption, family history	Stroke morbidity and mortality 378 cases	Adjusted RR (95% CI) (1) 1.0 (referent) (2) 0.76 (0.59–0.98) (3) 0.54 (0.38–0.76) (4) 0.78 (0.53–1.15) (5) 0.82 (0.58–1.14) Trend *P* = 0.05
Sacco et al., 1998 (59)	*N* = 489 men and 618 women Matched case-control study	Self-reported recreational physical activities Intensity (1) None (2) Light/moderate (3) Heavy Duration (h·wk^{-1}): (1) None (2) <2 (3) 2–5 (4) ≥5	Age, sex, race, hypertension, diabetes, cardiac disease, smoking, alcohol consumption	Cerebral infarction morbidity Men 163 cases Women 369 cases	Adjusted OR (95% CI or *P*-value) Physical activity intensity (1) 1.0 (referent) (2) 0.39 (0.26–0.58) (3) 0.23 (0.10–0.54) Physical activity duration (1) 1.0 (referent) (2) 0.42 (*P* < 0.05) (3) 0.35 (*P* < 0.05) (4) 0.31 (*P* < 0.05) Trend *P* = 0.006

TABLE 2. *Continued*

Study	Population/Design	Physical Activity Assessment	Adjusted for	Outcome	Summary of Results
Gillum et al., 1996 (23)	N = 5852 men and women Observational cohort study	Self-reported recreational and nonrecreational physical activity (1) Low (2) Moderate (3) High	Age, smoking, diabetes, heart disease, education, systolic blood pressure, cholesterol, BMI, hemoglobin	Stroke morbidity and mortality 623 cases	Adjusted RR (95% CI) (high level physical activity as a reference level) Recreational physical activity Men / Women 45–64 yr (1) 1.24 (0.63–2.41) / 3.13 (0.95–10.32) (2) 1.17 (0.61–2.27) / 1.80 (0.52–6.22) Trend $P > 0.05$ / $P = 0.008$ 65–74 yr (1) 1.29 (0.88–1.88) / 1.55 (0.95–2.53) (2) 0.86 (0.58–1.28) / 1.27 (0.76–2.12) Trend $P > 0.05$ / $P = 0.02$ Nonrecreational physical activity Men / Women 45–64 yr (1) 1.07 (0.40–2.86) / 3.51 (1.66–7.46) (2) 1.75 (1.04–2.96) / 1.07 (0.57–1.99) Trend $P > 0.05$ / $P = 0.01$ 65–74 yr (1) 1.82 (1.15–2.88) / 1.82 (1.10–3.02) (2) 1.20 (0.88–1.64) / 1.42 (1.01–2.00) Trend $P = 0.02$ / $P = 0.01$
Abbott et al., 1994 (1)	N = 7530 men Observational cohort study	Self-reported physical activity Physical activity levels (index) (1) Inactive (2) Partially active (3) Active	Systolic blood pressure, cholesterol, smoking, alcohol consumption, serum glucose, serum uric acid, hematocrit	Stroke morbidity and mortality 60 cases	Adjusted RR (95% CI) Thromboembolic stroke (age 55–68 yr) Nonsmoker / Smoker (1) 2.8 (1.2–6.7) / 1.2 (0.7–2.1) (2) 2.4 (1.0–5.7) / 0.7 (0.4–1.3) (3) 1.0 (referent) / 1.0 (referent) Hemorrhagic stroke 45–54 yr / 55–68 yr (1) 2.0 (0.8–5.1) / 3.7 (1.3–10.4) (2) 1.1 (0.4–3.3) / 2.2 (0.8–6.4) (3) 1.0 (referent) / 1.0 (referent)
Kiely et al., 1994 (33)	N = 2336 men and 2873 women Observational cohort study	Self-reported leisure or work physical activity Physical activity index tertiles (1) Tertile 1 (lowest) (2) Tertile 2 (3) Tertile 3 (highest)	Age, systolic blood pressure, cholesterol, smoking habit, glucose intolerance, total vital capacity, BMI, left ventricular hypertrophy, fibrillation, valvular disease, heart failure, heart disease, occupation	Stroke morbidity 1954–55 Men: 188 cases Women: 214 cases 1968–72 Men: 107 cases Women: 127 cases	Adjusted RR (95% CI) Men / Women Physical activity at exam 1954–55 (1) 1.0 (referent) / 1.0 (referent) (2) 0.90 (0.62–1.31) / 1.21 (0.89–1.63) (3) 0.84 (0.59–1.18) / 0.89 (0.60–1.31) Physical activity at exam 1968–1972 (1) 1.0 (referent) / 1.0 (referent) (2) 0.41 (0.24–0.69) / 0.97 (0.64–1.47) (3) 0.53 (0.34–0.84) / 1.21 (0.75–1.96)
Haheim et al., 1993 (26)	N = 14,403 men Observational cohort study	Self-reported physical activity (1) Sedentary (2) Moderate (3) Intermediate+great	None	Stroke morbidity and mortality 26 deaths 81 cases	RR (95% CI) Incidence / Mortality Physical activity at work (1) 1.0 (referent) / 1.0 (referent) (2) 0.66 (0.34–1.23) / 0.98 (0.33–2.69) (3) 1.62 (0.95–2.75) / 1.38 (0.46–3.81) Trend $P > 0.05$ / $P > 0.05$ Physical activity at leisure (1) 1.0 (referent) / 1.0 (referent) (2) 0.64 (0.38–1.08) / 0.82 (0.33–2.35) (3) 0.36 (0.15–0.80) / 0.29 (0.03–1.51) Trend $P > 0.10$ / $P > 0.09$
Herman et al., 1983 (28)	N = 235 men and 136 women Case-control study	Self-reported leisure physical activity (1) Little (2) Regular light (3) Regular heavy	Education, acute myocardial infarction, cardiac arrhythmia, high blood pressure, diabetes, obesity, transient cerebral ischemic attack, rhesus factor	Stroke morbidity Men: 83 cases Women: 49 cases	Adjusted OR (95% CI) (1) 1.0 (referent) (2) 0.49 (0.31–0.77) (3) 0.24 (0.10–0.59)
Change in physical activity					
Paffenbarger et al., 1998 (53)	N = 17,815 men Observational cohort study	1962/66 to 1977 (kcal·wk^{-1}) (1) increase ≥1250 (2) increase 750–1249 (3) increase 250–749 (4) unchanged (±249) (5) decrease 250–749 (6) decrease 750–1249 (7) decrease ≥1250)	Age, smoking habit, blood pressure status, body mass index, alcohol intake, parents dead before age 65 years, and chronic disease	All-cause mortality N = 4399	Adjusted RR (P-value) (1) 0.80 (<0.001) (2) 0.80 (0.003) (3) 0.93 (0.247) (4) 1.0 (referent) (5) 1.0 (0.934) (6) 1.15 (0.058) (7) 1.26 (0.001)

TABLE 3. Summary of studies on the dose-response relation of cardiorespiratory fitness to morbidity and mortality.

Study	Population/Design	Physical Fitness	Adjusted for	Outcome	Results
Farrell et al., 1998 (20)	N = 25,341 adult men Observational cohort study from 1970 to 1989 Average follow-up of 8.4 yr	Maximal exercise test on treadmill using a modified Balke protocol Cardiorespiratory fitness categories based on total treadmill time at baseline (1) Low fitness—least-fit 20% of each age group (2) Moderate fitness—next 40% of each age group (3) High fitness—remaining 40% of each age group	CVD mortality predictors included smoking, elevated systolic blood pressure, and elevated blood cholesterol	CVD mortality 226 deaths	Fitness category — CVD deaths/10,000 py 0 Mortality predictors (1) 14.1 (2) 4.2 (3) 4.5 1 Mortality predictor (1) 19.4 (2) 11.6 (3) 9.3 2–3 Mortality predictors (1) 21.7 (2) 20.5 (3) 10.2 Low fitness trend test P = 0.001 Moderate fitness trend test P = 0.004 High fitness trend test P = 0.325
Blair et al., 1996 (9)	N = 25,341 men Observational cohort study from 1970 to 1989	Maximal exercise test on treadmill using a modified Balke protocol Cardiorespiratory fitness categories based on total treadmill time at baseline (1) Low fitness—least-fit 20% of each age group (2) Moderate fitness—next 40% of each age group (3) High fitness—remaining 40% of each age group	Age, examination year, and other risk predictors	All-cause mortality 601 deaths	All-cause mortality **Deaths/10,000 py are estimated from Figure 3 in the paper Men Fitness category — Deaths/10,000 py 0 Mortality predictor (1) 28 (2) 18 (3) 17 1 Mortality predictor (1) 43 (2) 27 (3) 26 2–3 Mortality predictor (1) 57 (2) 42 (3) 25
Blair et al., 1991 (10)	N = 12,056 men 10,224 healthy normotensive men 1832 men with history of hypertension Observational cohort study from 1970–1985 Average follow-up 8 yr	Maximal exercise test on treadmill using a modified Balke protocol Cardiorespiratory fitness categories: treadmill time used to assign men to physical fitness quintiles (Q1 = least fit to Q5 = fittest)	Age	All-cause mortality Normotensive: 240 deaths Hypertensive: 78 deaths	Adjusted RR (95% CI) Normotensive men Quintiles Q1 3.4 (2.1–5.8) Q2 1.4 (0.8–2.5) Q3 1.5 (0.8–2.6) Q4 1.1 (0.6–2.2) Q5 1.0 (referent) Hypertensive men Q1 4.5 (2.9–6.9) Q2 1.2 (0.7–2.0) Q3 1.6 (1.0–2.7) Q4 2.4 (1.5–3.8) Q5 1.0 (referent)
Blair et al., 1989 (13)	N = 10,224 men and 3120 women Observational cohort study from 1970 to 1981 Average follow-up 8 yr	Maximal exercise test on treadmill using a modified Balke protocol Cardiorespiratory fitness categories: treadmill time used to assign men to physical fitness quintiles (Q1 = least fit to Q5 = fittest)	Age	All-cause mortality Men: 240 deaths Women: 43 deaths	Adjusted RR (95% CI) Men Q1 3.44 (2.05–5.77) Q2 1.37 (0.76–2.50) Q3 1.46 (0.81–2.63) Q4 1.17 (0.63–2.17) Q5 1.0 (referent) Women Q1 4.65 (2.22–9.75) Q2 2.42 (1.09–5.37) Q3 1.43 (0.60–3.44) Q4 0.76 (0.27–2.11) Q5 1.0 (referent)
Ekelund et al., 1988 (16)	N = 3106 healthy men (30–69 yr) Follow-up study	Submaximal treadmill exercise test using a modified Bruce protocol Fitness categories in quartiles based on heart rate taken during stage 2 of the exercise test: Q1-least fit to Q4-most fit		CHD and CVD mortality 45 deaths	CHD mortality Unadjusted Cumulative Mortality — 95% CI Q1 1.69 (0.77–2.61) Q2 0.91 (0.24–1.58) Q3 0.91 (0.24–1.58) Q4 0.26 (0.00–0.62) CVD mortality Unadjusted Cumulative Mortality — (95% CI) Q1 2.21 (1.16–3.25) Q2 1.56 (0.68–2.44) Q3 1.30 (0.49–2.11) Q4 0.26 (0.00–0.62)

TABLE 3. *Continued*

Study	Population/Design	Physical Fitness	Adjusted for	Outcome	Results
Lie et al., 1985 (45)	*N* = 2014 healthy men (40–59 yr of age) 7-yr follow-up study	Cycle ergometer test symptom-limited Fitness categories were determined by quartiles of cumulative work on the exercise test Q1-least fit to Q4-fittest		CHD mortality 58 deaths	Death rates Q1 5.74 Q2 2.38 Q3 2.20 Q4 1.19
Sandvik et al., 1993 (60)	*N* = 1960 healthy men Observational cohort study from 1972 to 1989 Average follow-up time 16 yr	Maximal exercise test on an electrically braked bicycle ergometer Cardiorespiratory fitness categories: change in fitness scores between the exams divided into quartiles (Q1 = least change, Q4 = most change)	Age and other risk factors	All-cause and CVD mortality 271 deaths 143 CVD deaths	Adjusted RR (95% CI) All-cause Q1 1.0 (referent) Q2 0.92 (0.66–1.28) *P* = 0.58 Q3 1.00 (0.71–1.41) *P* = 0.92 Q4 0.54 (0.32–0.89) *P* = 0.015 CVD Q1 1.0 (referent) Q2 0.59 (0.28–1.22) *P* = 0.15 Q3 0.45 (0.22–0.92) *P* = 0.026 Q4 0.41 (0.20–0.84) *P* = 0.013
Effects of change in fitness on morbidity and mortality					
Erikssen et al., 1998 (18)	*N* = 2014 healthy men (1st exam) 1756 participated in the 2nd exam Observational cohort study from 1972 to 1994 Interval between 1st and 2nd exam 7 yr Total follow-up time 22 yr	Maximal exercise test on an electrically braked cycle ergometer Cardiorespiratory fitness categories: Baseline fitness categories based on quartiles of fitness at 1st exam: Q1 (PF1) to Q4 (PF1) Change in fitness scores between 1st and 2nd exams divided into quartiles Q1-least change to Q4-most change	Age and other risk factors	All-cause mortality 1428 deaths	Standard Mortality Ratios All-cause Baseline Q1 (PF1) Q2 (PF1) Q3 (PF1) Q4 (PF1) Change in fitness scores Q1 1.22 1.19 0.87 0.73 Q2 0.80 0.77 0.62 0.46 Q3 0.72 0.33 0.60 0.17 Q4 0.47 0.43 0.40 0.17
Blair et al., 1995 (12)	*N* = 9777 men Observational cohort prospective study from 1970 to 1989 Average follow-up of 4.9 yr between 1st and 2nd examination Average follow-up for mortality was 5.1 yr after 2nd examination	Maximal exercise test on treadmill using a modified Balke protocol Cardiorespiratory fitness categories of quintile classifications at each exam and for some analyses Unfit = least-fit 20% of each age group Fit = all others Fitness categories after both examinations (1) Unfit-unfit (2) Unfit-fit (3) Fit-unfit (4) Fit-fit	Age	All-cause and CVD mortality 223 deaths 87 CVD deaths	Adjusted RR (95% CI) All-cause mortality (1) 1.0 (referent) (2) 0.56 (0.41–0.75) (3) 0.52 (0.38–0.70) (4) 0.33 (0.23–0.47) Quintiles Visits 1st 2nd RRs (95% CI) 2–3 2–3 1.0 (referent) 2–3 4–5 0.85 (0.56–1.29) 4–5 4–5 0.71 (0.46–1.09) CVD mortality (1) 1.0 (referent) (2) 0.48 (0.31–0.74) (3) 0.43 (0.28–0.67) (4) 0.22 (0.12–0.39) Visits 1st 2nd RRs (95% CI) 2–3 2–3 1.0 (referent) 2–3 4–5 0.72 (0.37–1.38) 4–5 4–5 0.48 (0.23–1.01)

especially Table 2, are already large, and we thought that we had enough data to address our questions without including nonfatal disease outcomes. We made one exception to this delimitation. We included one study in Table 4 on functional limitation as the outcome because we otherwise had only eight articles for this table, and several of them were relatively small.

Identifying source material. Our objective was to identify articles in the peer-reviewed literature that included data on at least one of the outcomes and on three or more levels of one or both of the exposure variables. To address questions 1 and 2, we reviewed studies that included assessments of either physical activity or cardiorespiratory fitness. Studies used to address question 3 were required to have data on both activity and fitness. Because there are many studies with physical activity and because these studies have been thoroughly reviewed recently (51,54,69), we restricted our review of studies to articles published in 1990 or later. Table 1 includes a summary of how material was selected for review.

Critical analysis of articles. At least two, and often all three, authors read each of the 67 articles on the final list. We summarized results in tabular form, with one table for each of the questions addressed in this report. Each table includes information on characteristics of the study population, method of assessing physical activity or fitness, information on confounding variables, and summary of study outcomes with an emphasis on the dose-response gradient. We used the evidence-based approach for rating the quality of the evidence

TABLE 4. Summary of 9 studies with assessments of both physical activity and fitness on the does-response relation to health outcomes.

Study	Population	Physical Activity or Fitness	Adjusted for	Outcome	Results
Huang et al., 1998 (30)	N = 3495 men and 1175 women Observational cohort study	Cardiorespiratory fitness Maximal exercise treadmill test (1) Low fit = least fit 20% (2) Moderate = 21–60% (3) High fit = 61–100% Self-reported leisure physical activity (I) Sedentary (none) (II) Moderate activity (walking or jogging <10 miles·wk^{-1} or other activity) (III) High active (walking or jogging ≥10 miles·wk^{-1})	Age, BMI, smoking, alcohol consumption, health status	Functional limitation	Adjusted OR (95% CI) Cardiorespiratory fitness Men / Women (1) 1.0 (referent) / 1.0 (referent) (2) 0.4 (0.2–0.6) / 0.5 (0.3–0.7) (3) 0.3 (0.2–0.4) / 0.3 (0.2–0.5) Physical activity Men / Women (I) 1.0 (referent) / 1.0 (referent) (II) 0.7 (0.5–0.9) / 0.7 (0.5–1.1) (III) 0.5 (0.3–0.8) / 0.7 (0.4–1.2)
Villeneuve et al., 1998 (71)	N = 6246 men and 8196 women Observational cohort study	Cardiorespiratory fitness Maximum of 3 stages of climbing steps for 3 min per stage (1) Undesirable (2) Minimum (3) Recommended Self-reported leisure activities kcal·kg^{-1}·d^{-1} (I) 0–0.5; (II) 0.5–1.5; (III) 1.5–3.0; (IV) ≥3.0	Age, sex, smoking habit	All-cause mortality Men 614 deaths Women 502 deaths	Adjusted RR (95% CI) Cardiorespiratory fitness Men and Women (1) 1.52 (0.72–3.18) (2) 1.02 (0.69–1.51) (3) 1.0 (referent) Physical activity Men / Women (I) 1.0 (referent) / 1.0 (referent) (II) 0.81 (0.59–1.11) / 0.94 (0.69–1.30) (III) 0.79 (0.54–1.13) / 0.92 (0.64–1.34) (IV) 0.86 (0.61–1.22) / 0.71 (0.45–1.11)
Kampert et al., 1996 (31)	N = 25,341 men and 7080 women Observational cohort study	Cardiorespiratory fitness Maximal exercise treadmill test (1) Quintile 1 (lowest) (2) Quintile 2 (3) Quintile 3 (4) Quintile 4 (5) Quintile 5 (highest) Self-reported leisure physical activity (miles·wk^{-1}) (I) Sedentary (II) 1–10 (III) 11–20 (IV) 21–40 (V) >40	Age, examination year, smoking, chronic illnesses, ECG abnormalities	All-cause and cancer mortality Men 601 deaths; 179 cancer Women 89 deaths; 44 cancer	Adjusted RR (95% CI) Cardiorespiratory fitness Men All-cause deaths / Cancer deaths (1) 1.0 (referent) / 1.0 (referent) (2) 0.55 (0.44–0.70) / 0.54 (0.35–0.84) (3) 0.61 (0.48–0.78) / 0.56 (0.36–0.87) (4) 0.52 (0.41–0.66) / 0.59 (0.38–0.90) (5) 0.49 (0.37–0.64) / 0.36 (0.21–0.61) Trend P = 0.001 / P = 0.001 Women All-cause deaths / Cancer deaths (1) 1.0 (referent) / 1.0 (referent) (2) 0.53 (0.30–0.95) / 0.63 (0.26–1.54) (3) 0.56 (0.31–1.01) / 0.76 (0.32–1.80) (4) 0.22 (0.10–0.49) / 0.38 (0.14–1.03) (5) 0.37 (0.19–0.72) / 0.47 (0.18–1.22) Trend P = 0.001 / P = 0.073 Physical activity Men All-cause deaths / Cancer deaths (I) 1.0 (referent) / 1.0 (referent) (II) 0.71 (0.58–0.87) / 0.71 (0.49–1.03) (III) 0.83 (0.59–1.16) / 0.42 (0.18–0.97) (IV) 0.57 (0.30–1.08) / 0.15 (0.02–1.12) (V) 0.92 (0.29–2.88) / (IV & V) Trend P = 0.011 / P = 0.002 Women All-cause deaths / Cancer deaths (I) 1.0 (referent) / 1.0 (referent) (II) 0.68 (0.39–1.17) / 0.84 (0.38–1.88) (III) 0.39 (0.09–1.65) / 0.95 (0.21–4.37) (IV & V) 1.14 (0.27–4.80) / 2.85 (0.62–13.16) Trend P = 0.217 / P = 0.557
Oliveria et al., 1996 (52)	N = 12,975 men Observational cohort study	Cardiorespiratory fitness Maximal exercise treadmill test (min) (1) <13.7 (2) 13.7–17 (3) 17.0–21.0 (4) ≥21.0 Self-reported leisure physical activity (kcal·wk^{-1}) (I) <1000 (II) 1000–2000 (III) 2000–3000 (IV) ≥3000	Age, BMI, smoking	Prostate cancer 94 cases	Adjusted RR (95% CI) Cardiorespiratory fitness (1) 1.0 (referent) (2) 1.10 (0.63–1.77) (3) 0.73 (0.41–1.29) (4) 0.26 (0.10–0.63) Trend P = 0.0036 Physical activity (I) 1.0 (referent) (II) 0.37 (0.17–0.79) (III) 0.62 (0.27–1.41) (IV) 0.37 (0.14–0.98) Trend P = 0.8263
Lakka et al., 1994 (36)	N = 1453 men Observational cohort study	Cardiorespiratory fitness Maximal oxygen uptake (L·min^{-1}) (1) <2.2 (2) 2.2–2.7 (3) >2.7 Self-reported leisure physical activity (h·wk^{-1}) (I) <0.7 (II) 0.7–2.2 (III) >2.2	Age, year of examination, height, weight, season of examination, type of respiratory-gas analyzer used	Acute myocardial infarction morbidity and mortality 57 cases	Adjusted RR (95% CI) Cardiorespiratory fitness (1) 1.0 (referent) (2) 0.76 (0.38–1.50) (3) 0.26 (0.10–0.68) Trend P = 0.006 Physical activity (I) 1.0 (referent) (II) 1.11 (0.58–2.12) (III) 0.31 (0.12–0.85) Trend P = 0.04

TABLE 4. *Continued*

Study	Population	Physical Activity or Fitness	Adjusted for	Outcome	Results
Blair et al., 1993 (11)	N = 10,224 men and 3120 women Observational cohort study	Cardiorespiratory fitness Maximal exercise treadmill test (1) Low fit, least fit 20% (2) Moderate, 21–60% (3) High fit, 61–100% Self-reported leisure physical activity (I) Sedentary (II) Moderate (III) Active	Age	All-cause mortality Men: 240 deaths Women: 43 deaths	Age adjusted RR (95% CI) Cardiorespiratory fitness Men / Women (1) 3.16 (1.92–5.20) / 5.35 (2.44–11.73) (2) 1.30 (0.73–2.32) / 2.22 (0.93–5.30) (3) 1.0 (referent) / 1.0 (referent) Trend P = 0.001 Physical activity Men / Women (I) 1.70 (1.06–2.74) / 0.95 (0.54–1.70) (II) 1.48 (0.9–2.42) / 0.75 (0.41–1.39) (III) 1.0 (referent) / 1.0 (referent) Trend P = 0.305
Hein et al., 1992 (27)	N = 4999 men Observational cohort study	Cardiorespiratory fitness Maximal cycle ergometer test (1) I (lowest quintile) (2) II (3) III (4) IV (5) V (highest quintile) Self-reported leisure physical activity (I) Low (rare or none) (II) Medium and high	Age	All-cause mortality 266 deaths	Age adjusted mortality for fitness In medium and high activity population (1) 17.0 (2) 15.9 (3) 16.5 (4) 18.5 (5) 12.5 Trend $P < 0.05$ In low activity population (1) 26.9 (2) 25.7 (3) 25.3 (4) 24.7 (5) 25.4 Trend $P > 0.05$
Arraiz et al., 1992 (4)	N = 13,379 men and women Observational cohort study	Cardiorespiratory fitness Using the observed and age, sex-specific reference pulse rates (1) Unacceptable (2) Acceptable (3) Recommended Self-reported physical activity Minutes in 2 wk (I) Inactive (0–1749) (II) Moderate (1750–2999) (III) Active (3000–5499) (IV) Very active (5500+)	Age, sex, smoking, alcohol consumption	All-cause, CVD, and cancer mortality 691 deaths men and women CVD: 256 men and women Cancer: 229 men and women	Adjusted RR (95% CI) Cardiorespiratory fitness All-cause deaths (1) 2.7 (1.4–5.5) (2) 1.6 (0.6–4.2) (3) 1.0 (referent) CVD deaths (1) 5.4 (1.9–15.9) (2) 0.8 (0.1–7.6) (3) 1.0 (referent) Cancer deaths (1) 1.9 (0.8–4.5) (2) 1.6 (0.4–5.4) (3) 1.0 (referent) Physical activity All-cause deaths (I) 1.5 (0.7–3.6) (II) 1.0 (0.4–2.8) (III) 1.5 (0.6–3.7) (IV) 1.0 (referent) CVD deaths (I) 0.9 (0.4–2.2) (II) 0.4 (0.01–1.0) (III) 1.0 (0.4–2.7) (IV) 1.0 (referent) Cancer deaths (I) 1.2 (0.7–1.9) (II) 0.8 (0.4–1.4) (III) 1.4 (0.8–2.3) (IV) 1.0 (referent)
Sobolski et al., 1987 (63)	N = 2363 men Observational cohort study	Cardiorespiratory fitness Defined as the work load at heart rate 150 beats·min^{-1} divided by body weight (kg) Quintiles (1) lowest to (4) highest Self-reported occupational and leisure physical activity metabolic index (I) lowest to (IV) highest	Age, HDL cholesterol, smoking, physical activity, systolic blood pressure, BMI	Ischemic heart disease incidences 31 cases	Incidence (%) cardiorespiratory fitness (1) 2.2 (2) 1.7 (3) 1.1 (4) 0.3 Trend $P < 0.05$ Incidence (%) physical activity Occupational / Leisure time (I) 1.6 / 1.2 (II) 1.0 / 1.7 (III) 1.5 / 1.3 (IV) 1.8 / 1.7 Trend $P > 0.05$ / $P > 0.05$ After controlling for other variables, physical fitness remained associated with incidence ($P < 0.05$)

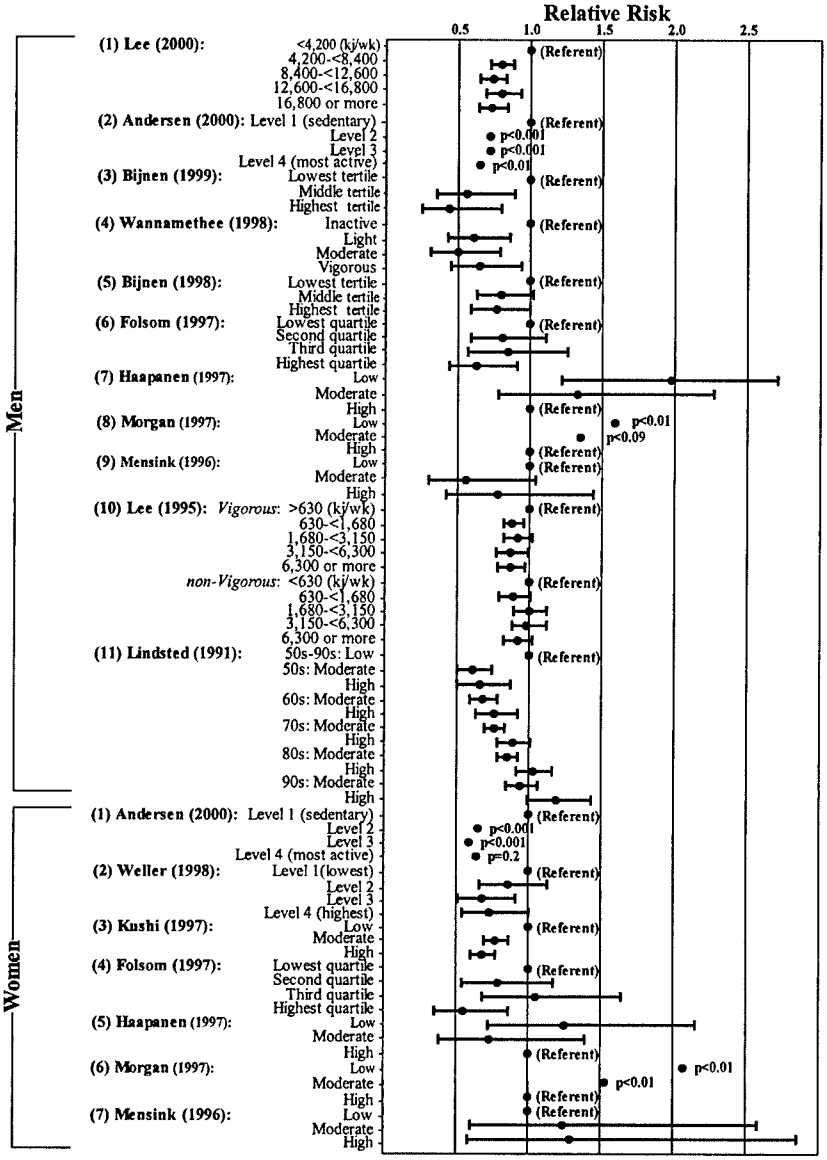


FIGURE 2—Dose-response for all-cause mortality across categories of physical activity in men (11 studies) and women (7 studies). Relative risks are shown for categories of physical activity. Note that the referent category in some studies is the least active group and for other studies is the most active group; 95% confidence intervals are included if they were available, otherwise only the point estimates (with *P*-values) are given. For some studies, point estimates are given for categories of physical activity within other strata (Lee et al. (38), by strata of vigorous and nonvigorous activity; Linsted et al. (46), by age groups).

discovered and summarized in the review. There are no randomized controlled clinical trials of either physical activity or fitness and the outcomes considered here, and thus the quality of evidence is Category C for each question we addressed.

RESULTS

Separate tables are presented for the dose-response associations of physical activity, fitness, or both exposures to the outcomes of morbidity and mortality.

Physical activity dose-response. Table 2 includes a summary of the evidence from 49 studies on the dose-response relation of physical activity to health outcomes. A majority of these papers have mortality as an outcome (CHD, CVD, stroke, site-specific cancer, or all-cause mortality); however, some studies include data on nonfatal chronic disease outcomes. Due to the large number of studies reviewed here with various health outcomes, vastly different approaches to assessing physical activity, and other methodological differences, it is not possible to accurately quantify a general dose-response gradient for physical activity. Nonetheless, and although there are exceptions (15,46,64), most studies show a general inverse dose-response gradient across physical activity categories for most health outcomes. The shape of the dose-response curves differ, but many of them show an asymptote, which suggests a threshold for benefits. Figure 2 shows point estimates for all-cause mortality by categories of activity for women (7 studies) and men (11 studies), respectively. In general, the point estimates for activity categories are more variable in women than in men, with one study in women (48) even showing nonsignificantly higher mortality in the more active women.

Cardiorespiratory fitness dose-response. Table 3 includes a summary of the evidence from nine studies on cardiorespiratory fitness and mortality (CHD, CVD, or all-cause mortality). There is remarkable consistency across studies, with all showing a strong inverse gradient of mortality across fitness groups. It should be noted that five of the nine studies are from the Aerobics Center Longitudinal Study (ACLS) data; and although these are from different

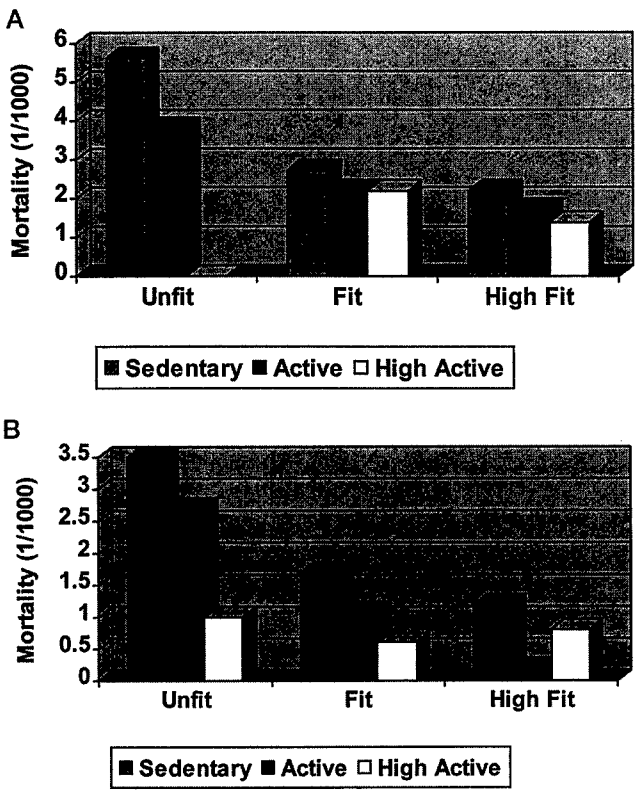


FIGURE 3—All-cause mortality rates by cardiorespiratory fitness and physical activity categories in 26,764 men (A) and 8755 women (B) participating in the Aerobics Center Longitudinal Study. Height of the bars represents the death rate per 1000 person-yr of observation. Death rates are based on 307,594 man-yr and 96,608 woman-yr of observation, and on 805 deaths in men and 146 deaths in women. Unfit participants are the least fit 20% in each age-sex group, fit are the next 40% of the fitness distribution, and high fit are the most fit 40%. Sedentary persons reported no physical activity, active individuals reported up to 19.9 MET·h^{-1} of physical activity per week, and high active individuals reported 20 or more MET·h^{-1}.

subgroups of the ACLS, one would expect to find similar results in these different analyses. The reports from the ACLS are the only ones to include women, and it appears that the association between fitness and mortality is similar in women and in men. Data are somewhat sparse, but the pattern of results is similar in normotensive and hypertensive men, and within different age groups.

Three of the studies included data on change in fitness from one examination to a second examination, with subsequent follow-up for mortality. Results from these studies are consistent with those from studies in which fitness was assessed only at baseline and study participants followed for mortality. Men who made greater improvements in fitness had greater reductions in mortality than was observed in men with little or no change in fitness.

The magnitude of reduction in mortality across fitness groups is substantial. Essentially all analyses show at least a 50% lower mortality rate in the high fit as compared with the low fit individuals. In some studies, the difference in mortality rates between the most and least fit individuals was on the order of three- to four-fold (10,13), and the difference was even greater in the report by Ekelund et al. (16).

Activity and fitness dose-response. Table 4 includes a summary of the evidence from nine studies that include both exposures of cardiorespiratory fitness and physical activity in relation to health outcomes. All studies show an inverse gradient across fitness categories for the various health outcomes, and most show an inverse gradient across physical activity categories. In general, the gradients are steeper for fitness than for activity. For example, the report by Arraiz et al. (4) shows RRs for all-cause mortality across three fitness groups of 2.7, 1.6, and 1.0 for the most fit; and RRs for all-cause mortality across activity groups in this study were 1.5, 1.0, 1.5, and 1.0 for the most active. A similar pattern was noted in the ACLS for women (11). None of the reports summarized in Table 4 include data from a multivariable model in which activity and fitness were both included. We included one report in Table 4 that had an outcome measure different from other studies in this review. Huang et al. (30) evaluated the relation of activity and fitness to the prevalence of functional limitations. These data show an inverse gradient across both activity and fitness groups in both men and women, and the gradients are steeper for fitness than for activity.

Aerobics Center Longitudinal Study. As shown in Table 4, there are only nine published reports from prospective studies meeting our inclusion criteria in which both physical activity and cardiorespiratory fitness have been assessed. Four of the studies summarized in Table 4 are from our ACLS database. We have recently extended mortality surveillance in our cohort and therefore decided to perform some preliminary analyses with our data specifically in relation to addressing question 3 established for this report.

From 1970 to 1994, there were 40,391 patients aged 20—90 yr who were examined at least once at the Cooper Clinic. We selected participants for these preliminary analysis who were healthy (no history of CVD, diabetes, or cancer and had a normal ECG) and achieved at least 85% of age-predicted maximal heart rate on the treadmill test. The 8755 women and 26,764 men who met these criteria were followed from the date of their baseline examination to date of death or to December 31, 1994, for survivors. These participants contributed 96,608 woman-yr and 307,594 man-yr of follow-up, during which 146 women and 805 men died. We assigned participants to three categories of physical activity based on their responses to their activity habits during the 3 months before their baseline examination. We calculated MET hours per week using Ainsworth et al.'s physical activity compendium (2) and assigned each participant to one of three activity categories: no reported activity = sedentary; up to 19.9 MET hours per week = active, and 20 or more MET hours per week = highly active. Study participants also were assigned to fitness categories based on age-sex treadmill time distributions: low fitness = least fit 20%, moderate fitness = next 40%, and high fitness = most fit 40%, as in our published studies referenced here.

We cross-tabulated the three activity and three fitness categories and calculated all-cause death rates per 1000 person-yr of observation (Fig. 3). There was an inverse

mortality gradient across both activity and fitness categories in both men and women. The highest death rates for both men and women were in the unfit-sedentary group and the lowest death rates were in the high fit-highly active group. We then submitted these data to a proportional hazards analysis, with physical activity, cardiorespiratory fitness, BMI, smoking habit, alcohol intake, and parental history of CVD included in the model. Physical activity was not associated with mortality in these analyses, but the inverse gradient across fitness groups remained, with a 50% reduction in mortality in the moderately fit women and men and a 70% reduction in the high fit individuals, when compared with those in the low fit category.

CONCLUSIONS

The review performed for this report focused on three specific questions. Evidence statements and a rationale are provided below for each of the questions. All statements are based on Category C Evidence.

1. Is there a dose-response relation between physical activity and health outcomes?

Evidence statement. Individuals who are regularly physically active are less likely than sedentary individuals to develop health problems. The inverse gradient of risk across activity groups is seen in different population groups and for fatal and nonfatal outcomes.

Rationale. Some health outcomes are probably not associated with physical activity habits, for example, rectal cancer. There is compelling evidence that regular physical activity extends longevity and reduces risk for CHD, CVD, stroke, and colon cancer. For these outcomes, there is consistent evidence for an inverse dose-response effect across physical activity groups. Data are not sufficient to determine whether the slope of the gradient is different for different health outcomes or whether the shape of the dose-response curve is linear or curvilinear.

2. Is there a dose-response relation between cardiorespiratory fitness and health outcomes?

Evidence statement. There is an inverse gradient across categories of cardiorespiratory fitness for risk of fatal and nonfatal health outcomes. The pattern of association between fitness and outcomes is highly consistent across studies.

Rationale. There are fewer studies on cardiorespiratory fitness and health than are available on physical activity and health; however, the fitness studies are compelling in their consistency and in the steepness of the dose-response gradient across fitness groups. Studies including measures of fitness are of necessity laboratory- or clinic-based and, thus, also usually have extensive and objective data on health status and potential confounding variables, such as data from clinical chemistry analyses, blood pressure, and body composition. Most of the studies show a curvilinear dose-response association for most outcomes, with an asymptote occurring in the upper part of the fitness distribution.

3. If both physical activity and cardiorespiratory fitness have a dose-response relation to health outcomes, is there a difference in the outcome gradient across categories for the two exposures, and is it possible to determine from the available data which exposure is more important for health?

Evidence statement. The dose-response gradient for various health outcomes is steeper across categories of cardiorespiratory fitness than across physical activity groups. In preliminary analyses from the ACLS, when activity, fitness, and possible confounding variables are included in a multivariate model, fitness remains strongly associated with mortality, and the association for activity and health is no longer significant.

Rationale. As indicated in the evidence statements for questions 1 and 2, data from existing studies indicate dose-response gradients across categories of activity and fitness for multiple health outcomes. It is not possible to determine from these studies whether one of the exposure variables is more important than the other as a predictor of health. Data in Table 4 suggest that fitness is more important than activity in relation to health outcomes; however, we do not think this is a valid conclusion. Physical activity is the principal determinant of cardiorespiratory fitness, although there is a genetic component. We think that the most likely explanation for the stronger dose-response gradient for fitness shown in Table 4 is that fitness is measured objectively and physical activity is assessed in the studies reviewed here by self-report, which inevitably leads to misclassification—often substantial misclassification. With activity usually producing greater misclassification rates than are seen for fitness, it follows that data from observational studies will typically show a stronger association between fitness and health outcomes than for activity and health outcomes.

ISSUES AND LIMITATIONS

The question posed in the title of this report is the major issue. This question has received attention over the past several years, which escalated after publication of the CDC/ACSM public health recommendation for physical activity (54). The focus of that recommendation was on *accumulating* activity of *moderate* intensity, and this approach was difficult for some to reconcile with prior exercise recommendations that emphasized continuous bouts of relatively vigorous exercise. Some individuals began to talk about two principal types of physical activity—activity for health benefits and activity for improving fitness. The underlying notion for this concept was apparently that low amounts and intensities of activity might improve health (reduce risk of morbidity or mortality) but not produce any improvements in fitness. Our view is that activity cannot be designated as either for health or for fitness. We submit that any physical activity that has the capacity to change either health or fitness will change both. It may well be that there are minimum amounts and intensities that are required for any physiological or psychological adaptations to occur, that specific adaptations may be produced by specific amounts and types of activity, and that it might require a large sample size to confirm that small changes in activity are associated with small changes in both health and fitness. Nonetheless,

we interpret a demonstrated dose-response relationship to mean that any change in dose will produce a known response. This leads to the conclusion that given a sufficiently large sample size, an increase in physical activity of 10 $kcal \cdot d^{-1}$ would lead to detectable increments of change in physiological and psychological variables that are affected by activity. Thus, we think that the focus should be on learning more about exercise dose-response relationships in general, rather than trying to determine whether physical activity or physical fitness is more important to health benefits.

From a public health policy perspective, it is clear that recommendations and programs should be designed to promote physical activity and not fitness. It would not make sense to encourage individuals to "become fit," but instead we can, and should, recommend that individuals "increase activity." We think it is likely that if sedentary persons do the latter, they will achieve the former.

Our review has limitations. We imposed the limitations of the selection criteria described earlier. These criteria limited the diseases, health conditions, and clinical outcomes considered and restricted the review to human studies. In addition, there were limitations resulting from the available literature. Current studies are limited by relatively few women and by severe limitations of racial/ethnic, socioeconomic, geographic, and other diversity characteristics.

RESEARCH RECOMMENDATIONS

Additional research is needed to address the issues discussed here. We do not think that it is important, or even desirable, to try to determine whether physical activity or cardiorespiratory fitness is more important for health. Fitness is developed by activity, although the magnitude of response to the exercise stimulus is genetically determined. Nonetheless, it seems likely that activity will be required to develop and maintain levels of fitness that are consistent with good health. Although we do not recommend additional research to pursue the elusive question posed in the title of this report, there are important studies that should be conducted.

1) Studies of both activity and fitness should focus on defining more precisely the shape of the dose-response curve. It is established that 30 min of moderate intensity activity on most days of the week will produce important health benefits. However, suppose that a person only participates in 15 min of moderate intensity activity per day. Will he or she receive any health benefits? Conversely, are additional health benefits expected if a person obtains 60 min of activity per day? These and other issues need further exploration in randomized controlled clinical trials.

2) It is clear that cardiorespiratory fitness, which is produced by aerobic exercise, has substantial health benefits. Musculoskeletal fitness, as developed by resistance exercise, clearly has benefits for preservation or regaining function. It is unclear whether resistance exercise training would reduce the risk of chronic diseases such as hypertension, CHD, or type 2 diabetes. Furthermore, if resistance training does affect risk of chronic disease, what is the shape of the dose-response curve? These issues need to be addressed in future research studies.

3) Although it is clear there is a dose-response relationship between both activity and fitness and several health outcomes, other outcomes need further research. Are activity and fitness inversely related to the risk of breast, prostate, and lung cancer; depression and anxiety disorders; psychotic episodes; gall bladder disease; or other health conditions that have not been studied?

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Absolute versus relative intensity of physical activity in a dose-response context

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ABSTRACT

SHEPHARD, R. J. Absolute and relative intensity of physical activity in a dose-response context. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S400–S418. **Purpose**: To examine the importance of relative versus absolute intensities of physical activity in the context of population health. **Methods**: A standard computer-search of the literature was supplemented by review of extensive personal files. **Results:** Consensus reports (Category D Evidence) have commonly recommended moderate rather than hard physical activity in the context of population health. Much of the available literature provides Category C Evidence. It has often confounded issues of relative intensity with absolute intensity or total weekly dose of exercise. In terms of cardiovascular health, there is some evidence for a threshold intensity of effort, perhaps as high as 6 METs, in addition to a minimum volume of physical activity. Decreases in blood pressure and prevention of stroke seem best achieved by moderate rather than high relative intensities of physical activity. Many aspects of metabolic health depend on the total volume of activity; moderate relative intensities of effort are more effective in mobilizing body fat, but harder relative intensities may help to increase energy expenditures postexercise. Hard relative intensities seem needed to augment bone density, but this may reflect an associated increase in volume of activity. Hard relative intensities of exercise induce a transient immunosuppression. The optimal intensity of effort, relative or absolute, for protection against various types of cancer remains unresolved. Acute effects of exercise on mood state also require further study; long-term benefits seem associated with a moderate rather than a hard relative intensity of effort. **Conclusions:** The importance of relative versus absolute intensity of effort depends on the desired health outcome, and many issues remain to be resolved. Progress will depend on more precise epidemiological methods of assessing energy expenditures and studies that equate total energy expenditures between differing relative intensities. There is a need to focus on gains in quality-adjusted life expectancy. **Key Words:** INTENSITY, DOSE OF EXERCISE, ASSESSMENT OF ENERGY EXPENDITURE

This paper examines the importance of relative versus absolute intensity of physical activity in the context of population health. The two variables are plainly interrelated and may be very similar to each other in a population that is relatively homogeneous with respect to age, gender, and fitness. In a more heterogeneous sample, the question becomes whether outcome is affected by relative intensity when people perform a given volume (absolute intensity · time) of physical activity. Most of the papers to be discussed refer to large muscle activities, but if the active muscle mass is small, relative intensities must be expressed in relation to the peak response to exercise involving this particular volume of muscle (221). Debate on the optimal pattern of health-enhancing physical activity has a long history (50,115,244). One early review of this question (211) concluded:

"Some workers, basing their views on personal experience of illness or on the one experimental study of bed rest (52), have contended that the ordinary routine of daily life produces considerable training. Others (14,32) have stated categorically that mild exercise, such as golf and bowling is not enough; a pulse rate of 140/min (60% of the maximum possible increase over the resting value (31,32)) or 150/min (34) is essential for training." (p. 533)

An experimental study from the same era (212) exposed 39 young sedentary men (predicted maximal oxygen intake 43.4 ± 5.8 mL·kg^{-1}·min^{-1}) to training that varied in intensity (39, 75, or 96% of aerobic power), frequency (1, 3, or 5 sessions per week), and duration (5, 10, or 20 min per session). Step-wise multiple regression analysis suggested that increments in maximal oxygen intake were significantly related to initial aerobic power (mL·kg^{-1}·min^{-1}), intensity of training (mL·kg^{-1}·min^{-1}), and the number of training sessions per week. This study found some response even at the lowest dose of training, but the magnitude of response was influenced most strongly by the intensity of training relative to the individual's personal level of aerobic fitness.

Early observers focused on enhancing maximal aerobic power and cardiovascular function, assuming that the needs of health would be satisfied thereby (2,12,25,37,60,64,70,76,81,83,109,138,168,183,210,213,237). An increase of physical fitness is indeed associated with a reduced risk of cardiovascular and all-cause mortality (22,23,62,199), and is important to maintaining functional independence and thus quality of life in the elderly (71,85,181,214,225,243). However, debate has shifted more

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recently to the minimal level of physical activity needed to achieve specific health-related outcomes, including a reduction in overall and cardiac mortality, the control of hypertension and the prevention of strokes, improvement of metabolic health (the control of obesity, blood glucose regulation, the prevention of diabetes mellitus, and optimization of lipid profile), control of osteoporosis, enhancement of immune function, reduction of the risk of various tumors, and enhancement of mental health. It seems unlikely that a single relative or absolute intensity of physical activity will meet all of these objectives (21,95), and the achievement of some outcomes is unlikely to require an increase of aerobic fitness (184). Where possible, semantic descriptions of intensity have been matched to those proposed by Howley (105). One cross-sectional study of some 350 people found that whereas gains in cardiovascular variables were correlated with perceptions of hard ("vigorous") physical activity (219), the control of body fat was associated with frequent, moderate physical activity.

The public policy issue of whether to advocate a moderate or a hard relative intensity of physical activity is far from resolved (92,130,161,217,218,255). Discussion has gathered new impetus over recent recommendations to incorporate necessary daily physical activity into "active living" rather than formal exercise classes (15,52,57,58,102,128,161,180,198,216,218,255,258). To date, those benefiting from everyday activities have tended to be sedentary, obese, and elderly people, those in whom a given absolute intensity of effort such as brisk walking develops a substantial relative intensity of effort (186,218). A table (p. 79) in one recent consensus document emphasized the major impact of an age-related decline in maximal oxygen intake on the relationship between absolute and relative intensity of effort (28), and an accompanying paper highlighted the need to distinguish absolute from relative intensity of physical activity (95). Subsequent modification of the table expressed aerobic intensities as a fraction of the oxygen consumption reserve (8,105,255). This change overcame the problem that resting metabolism accounts for a larger fraction of total energy expenditure in women, older men, and unfit individuals. It also made percentages of the individual's maximal aerobic potential more comparable with percentages of heart rate reserve or peak aerobic power output (140,178,239).

Many papers have continued to focus on absolute intensities, asking whether health outcomes are enhanced by some specific energy expenditure, measured in METs, METs·wk^{-1}, or kJ·min^{-1} (130,161). Assessments of both relative and absolute intensities of effort have been handicapped by limitations of field methodology. Field observers commonly lack the information needed to estimate relative intensities of effort. Moreover, the claim that cardiovascular health is enhanced above a threshold absolute energy expenditure of 2 MJ·wk^{-1} (171) is challenged by (i) potential errors of up to 2 MJ·wk^{-1} in estimates of gross weekly energy expenditures (217), and (ii) a failure to distinguish between gross costs (where a variable 1–2 MJ·wk^{-1} of imputed energy expenditure is due to normal resting expenditures) and net energy costs. In some cases, apparent differences in health outcome as large as 20% have remained statistically insignificant because of problems in measuring either physical activity or health (11,256). Analyses are further complicated because hard activity is usually recalled more readily and more precisely than light or moderate effort (3,135). If a given activity such as walking is randomly assigned, it may provoke reductions in unmeasured components of active leisure (190). Further, the reporting of certain patterns of physical activity reflects the attitudes and overall lifestyle of the individual (201,220), and if data are adjusted statistically for differences of lifestyle, previously observed associations between physical activity and health outcomes may disappear (110). Finally, the association of benefit with repeat reports of a given pattern of physical activity may indicate the importance of long-sustained active behavior (for example, in the prevention of neoplasia), but it may also reflect the greater accuracy of duplicate observations.

REVIEW TECHNIQUES

Published articles on the relationship between intensity of physical activity and health benefits have commonly included as key-words exercise prescription, training load, exercise, prevention, energy expenditure, physical fitness and health, intensity, exercise and health (education, policy, promotion and public), absolute intensity (exercise-physiology), and relative intensity (oxygen consumption-physiology). The majority of relevant papers before 1995 were identified in an earlier search (216). The current search of MEDLINE spanned the period from 1991 through December of 1999. Over this period, 1666 papers discussed exercise + intensity and 770 exercise intensity, but a combination of intensity + exercise + health yielded only 24 citations. Likewise, absolute exercise intensity yielded 7528 citations, but when this was combined with health, the total dropped to 52. Relative intensity yielded 4441 papers, but this was reduced to 5 citations on adding the term health. The Sport Discus was reviewed for the period from January of 1995 to September 1999. Given its exercise orientation, the search was limited to exercise prescription, intensity and health; this yielded 130 hits. The papers thus identified were supplemented by those identified in the earlier search, items garnered from major reviews (8,20,27,95,96,132,161,166,174,179,180,255,265) and material in extensive personal files. Because of geographic constraints, articles were reviewed only by the present author.

A large proportion of the papers thus identified merely asserted that a certain relative or absolute energy expenditure had a beneficial influence on health (217,218). The present review was limited to the 176 articles that sought evidence of a threshold of relative or absolute intensity of effort. Unfortunately, the importance of relative versus absolute energy expenditure was often obscured even in these articles, because differing relative intensities of effort were not matched for total weekly energy expenditures.

TABLE 1. Consensus panel judgments on intensity of physical activity needed to enhance health.

Author	Objective and Recommended Pattern of Physical Activity
Am. Assoc. Cardiovascular and Pulmonary Rehabilitation (5)	Cardiac rehabilitation; >50% of exercise capacity
American College of Sports Medicine (6)	Treatment of hypertension; 40–70% $\dot{V}O_{2max}$; resistive training added only as a part of comprehensive fitness program
American College of Sports Medicine (7)	Tertiary treatment of coronary vascular disease; 40–85% $\dot{V}O_{2max}$
American College of Sports Medicine (8)	Increase of $\dot{V}O_{2max}$; minimum training intensity 40–50% of $\dot{V}O_2R$, progression to 85% of $\dot{V}O_2R$ in fit subjects (minimum duration of session depends on intensity) Muscle strengthening; maximal or near maximal tension development in resisted exercises Fat loss; absolute energy expenditure of 1.05–1.25 MJ per session Other aspects of health not considered
American Heart Association (24,66)	CVD prevention and rehabilitation: greatest benefit at lowest intensities of effort; added benefits at higher intensities; lifestyle activities recommended at 50–60% $\dot{V}O_{2max}$
American Medical Association (9)	Pediatric health promotion; moderate intensity of activity
Centers for Disease Control and ACSM (180)	Population health: moderate intensity of activity on most days, equivalent to 800 kJ accumulated over 30-min sessions; lifestyle activities emphasized; benefit suggested as proportional to cumulative absolute energy expenditure
Health Canada (98)	Population health promotion; begin with light effort and progress to moderate and hard ("vigorous") activities later if you like
Health Education Authority (U.K.) (99)	Population health promotion; moderate activity such as sustained brisk walk
International Federation of Sports Medicine (107)	Population health promotion; endurance activities such as walking, running, hiking, swimming, cycling, rowing, skating, or cross-country skiing. Choice depends on age and initial physical condition
International Pediatric Guidelines (197)	Pediatric health promotion; moderate or hard ("vigorous") physical activity
Kino-Québec (27)	Population health promotion; "moderate" intensity of exercise (40–60% of $\dot{V}O_{2max}$). If relative intensity is lower, duration must be prolonged. But relatively light intensity (<16 kJ · min^{-1}) protects against cardiovascular disease. Benefit in diabetes and obesity linked to absolute energy expenditure of >2MJ · wk^{-1}. In cancer, benefit increases with intensity of effort. Overall recommendation is for an absolute increase of 4–6 MJ · wk^{-1}
Ministry of Health and Welfare (Japan) (154)	Population health promotion; age-specific intensities
National Heart Foundation of Australia (164)	Cardiovascular health; any regular physical activity beneficial; health benefits decrease and risks increase at very high intensities of effort
NIH Consensus Development Panel (166)	Promotion of CV health; moderate intensity recommended, but additional health benefit from hard ("more vigorous") activity
Obesity Consensus Conference (26)	Control of obesity; intensity not specifically discussed, but emphasis on absolute expenditures
Québec Consensus Conference (94)	Population health; effects of intensity need further investigation; graded response to amount, and (for some outcomes) to intensity of effort
Royal College of Physicians (252)	Regular recreational exercise
Toronto Consensus Conference (96)	Absolute intensity important for weight loss; optimal intensity not decided for many health outcomes
US Department of Health and Human Services (255)	"Moderate" intensity of activity
World Health Organization (19)	Emphasis on walking and cycling
WHO, Int. Soc. & Fed. of Cardiology (17)	Regular light-to-moderate activity
World Hypertension League (63)	Endurance activities, beginning at light to moderate intensity

Heavy physical activity can have potential negative effects (musculoskeletal injuries (185), cardiac incidents (227,257), immune suppression (215), and overtraining (123)). Such outcomes reduce the *net* health benefits of physical activity. Nevertheless, the relative intensities inducing such outcomes are large and, thus, have only limited importance for the average sedentary adult who is initiating a program of moderate physical activity. These risks are not given detailed consideration in the present review.

CURRENT STATUS OF KNOWLEDGE

Consensus conferences. At least 23 national and international consensus reports have been published over the past 10 yr (Table 1). Some of these documents have looked at specific outcomes such as hypertension (63), obesity (26), or the secondary or tertiary prevention of coronary disease (232), but most have taken a global approach to health (29,30). The emphasis has been on survival rather than quality-adjusted life expectancy, and there has been little attempt to evaluate the relative importance of competing outcomes. Often, a minimum *duration* of activity has been recommended for any given relative intensity of effort. Thus, *de facto* a minimum-condition–related volume of physical activity has also been specified. With a few exceptions (27,107,154), consensus documents generally have not discussed the importance of relative versus absolute intensity of physical activity.

Conclusions. Almost all expert groups (Category D Evidence) except those concerned with adolescents (9,197) and obesity (26) have concluded that a light to moderate intensity of aerobic activity (40–60% of $\dot{V}O_{2max}$; 40–50% of $\dot{V}O_2R$) is an appropriate minimal recommendation for population health (Table 1). However, the power of this apparent unanimity of opinion is weakened by a large overlap in membership among various expert groups. Some reports (8,98) have noted additional health benefits when people have progressed to a higher intensity of effort (up to 85% of $\dot{V}O_{2max}$ or $\dot{V}O_{2max}R$), but many recent reports have argued that "active living" offers an adequate minimum of physical activity. Meta-analyses further indicate that, at least initially, a light-to-moderate intensity of physical activity is most effective in motivating sedentary individuals (55,61,103,207). Unfortunately, only a few consensus groups (27,107,154) have examined the issue of relative versus absolute intensity of effort.

PHYSICAL ACTIVITY VERSUS ALL-CAUSE OR CARDIOVASCULAR MORTALITY OR CARDIAC RISK FACTORS

Much early research on all-cause or cardiovascular mortality was based on cross-sectional occupational compari-

sons, where at best it was possible to distinguish light from hard physical work (255). Occupational studies are not considered in the present report, in part because of a substantial fitness-related selection into and out of heavy employment (162,267), and in part because the categorization of intensity of effort is very different for 30 min of leisure activity and an 8-h working day. Thirty-three reports covering 29 studies of leisure behavior have been examined (Table 2). All are large-scale longitudinal observational surveys, where correlations have been sought between simple questionnaire estimates of physical activity and health outcomes. In 16 of these studies, the reported type, frequency, intensity, and duration of physical activity have been combined to yield semiquantitative estimates of weekly energy expenditures, sometimes described erroneously as "intensity" of effort. Analyses of the Harvard Alumni data suggest that both total and cardiovascular mortality are reduced progressively over the weekly energy expenditure range 2.1–8.4 $MJ \cdot wk^{-1}$ (172,173).

Fifteen reports (13 studies) have looked specifically at cross-sectional differences in outcome between individuals who reported hard physical activity versus those who did not (18,67,77,126,133,135,143,152,159,160,172,173,195,208, 209,229). Although the intent seems to have been to compare relative intensities, the threshold for benefit has commonly been reported as an absolute power output, and with a few exceptions (18,135,159,160,175), the influence of relative or absolute intensity of activity has not been distinguished from associated changes in the total volume of physical activity. The majority of studies have pointed to a threshold intensity of 6 METs (126,135,159,160,172,229) or more (152). Nevertheless, some comparisons between moderate and hard physical activity have found health benefits from light to moderate intensities of effort (18,143,195). Furthermore, as discussed below, hypertensive subjects seem at increased risk during hard intensities of effort (208,209), perhaps because there is a disproportionate increase in catecholamine secretion during hard physical activity (254). Unfortunately, there have been few studies in the absolute intensity range recently recommended by many expert groups (4–6 METs).

Some analyses of one study suggested additive effects from the intensity and the absolute volume of physical activity (133,135,172); other investigators noted an effect of intensity independent of volume (159,160) or an effect of duration independent of intensity (18). Further, a cross-sectional comparison found that occasional activity >6 METs (<once per week) was associated with a 107-fold increase in the immediate risk of a myocardial infarction in the first hour postexercise, as compared with a 2.4-fold increase of risk in those pursuing the same intensity of effort five or more times per week (155).

A total weekly energy expenditure of 8.4 MJ seems necessary to regression of atherosclerotic lesions (91). Several small crossover laboratory trials (Category B Evidence) have looked at acute changes in clotting mechanisms (156,226,240,262). With one exception (259), these have suggested that benefit is much greater with hard than with moderate intensity physical activity.

Conclusions. A substantial proportion of available reports have noted that a threshold absolute intensity of physical activity of around 6 METs is needed for all-cause or cardiovascular benefit (Category C Evidence). Unfortunately, this threshold has not been related to maximal aerobic power, so the relative intensity of physical activity remains unclear. Moreover, most studies have not distinguished effects of relative or absolute intensity independently of associated changes in the volume of physical activity.

PHYSICAL ACTIVITY, CONTROL OF HYPERTENSION AND STROKE

Three small-scale crossover trials (69,141,146) and one large cross-sectional analysis (265) have explored the acute impact of various intensities of physical activity upon blood pressures (Table 3). The crossover studies agree that the immediate reduction of blood pressure is independent of the relative intensity of effort, but in the cross-sectional analysis, the velocity of running (and thus intensity) had a much greater impact than the volume of activity as indicated by the distance covered.

Eleven of 15 studies of physical activity and chronic reductions in blood pressure involve small samples of randomly assigned subjects; three of the remaining four are large-scale nonrandomized longitudinal studies (Table 3). Five investigators have found a U-shaped relationship, with less benefit at high than at lower relative intensities of effort (47,88,121,148,192). Possibly, adoption of too high an intensity of effort reduced the impact of physical activity upon associated risk factors such as obesity and blood lipid profile. In contrast, five reports noted no effect of intensity (31,59,157,193,241). Three other reports observed an increase of response with intensity of effort (56,68,86); in one of these (56), walking distance was controlled. One of the cross-sectional studies (177) observed a threshold volume of activity for benefit (8.4 $MJ \cdot wk^{-1}$), but it did not examine the importance of relative vs absolute intensity of effort in reaching this threshold.

Five large-scale nonrandomized longitudinal data sets and two case-control studies have looked at the influence of physical activity upon stroke. Two reports (139,151) support suggestions of a U-shaped relationship to the intensity of effort (41), with little long-term benefit beyond an intensity of 70% of $\dot{V}O_{2max}$ (90). One of the remaining reports found no effect of intensity (118), and the other four (101,173,196,260) observed an increased response with greater amounts of effort, but in none of these four studies was volume controlled.

One major weakness in research to date has been a failure to differentiate between hemorrhagic and ischemic strokes. Physical inactivity is apparently a risk factor in all cases of hemorrhagic stroke, but in ischemic stroke, this is true only of smokers (1). In some studies, there has also been a failure

TABLE 2. Physical activity versus mortality, cardiovascular mortality, or cardiac risk factors.

Author	Sample	Design	Program	Response
Effects of intensity of physical activity				
Paffenbarger et al. (175)	17,815 M aged 45–84 yr (Harvard Alumni)	L	16-yr follow-up of deaths	Deaths for any given volume of exercise less with participation in moderately intense sport than for lighter activities
Lee et al. (135)	17,321 M aged 46 yr free from CVD, cancer, or chronic obstructive lung disease (Harvard Alumni)	L	22 to 26-yr follow-up, mortality rate vs absolute intensity of activity (>6 METs)	Relative to energy expenditure <630 kJ · wk^{-1}; light-moderate activity, no significant effect. Moderate-hard ("vigorous") activity 630–1680 kJ · wk^{-1}, RR 0.88; 1680–3150 kJ · wk^{-1}, RR 0.91; 3150–6300 kJ · wk^{-1}, RR 0.87; >6300 kJ · wk^{-1}, RR 0.86
Lee et al. (133)	13,485 M aged 57.5 yr (Harvard Alumni)	L	Mortality vs walking and stair-climbing	Light activity-no effect on mortality. Suggestion of benefit 4–6 METs, clear benefit if >6 METs
Mensink et al. (152)	7689 M, 7747 F aged 25–69 yr	L	Total and CVD deaths	Relative to low level of leisure activity; significant only for hard activity (7.5–9.0 METs); RR in M 0.36 for total deaths, 0.26 for CVD; in F, NS due to insufficient incidents
Morris et al. (159,160)	9,376 M 45–64 yr Clinical CHD excluded at entry (British civil servants)	L	9-yr follow-up, incidence of CVD	Dose-related protection from hard ("vigorous") sport play but not from light-moderate ("non-vigorous") (age-adjusted data; vigorous = 7.5 kcal · min^{-1}, 6 METs); sample more fit than average British man). Relative to no hard ("vigorous") exercise, 2 bouts · wk^{-1} RR 0.36. No effect from number of episodes or energy expended in light-moderate ("non-vigorous") activity.
Folsom et al. (67)	7852 F, 6188 M 45–64 yr, biracial	L	4 to 7-yr follow-up, CHD incidence quartile classification of sport, leisure	Highest relative to lowest quartile sport, RR 0.56 (F), 0.60 (M); leisure activity, RR 0.51 (F), 0.62 (M); heavy intensity sport, RR 0.31 (F), 0.43 (M). No benefit from active commuting > 30 min · d^{-1}
Shaper and Wannamethee (208)	7630 M aged 40–59 yr (British General Practice)	L	8-yr follow-up, incidence of CHD in relation to activity index	Relative to hard ("vigorous") inactive, occasional or light activity RR 0.8, moderate or moderately hard ("moderately vigorous") RR 0.4, hard ("vigorous") RR 0.8 (all adjusted for age, BMI, SES, and smoking)
Shaper et al. (209)	5694 M aged 40–59 yr (British General Practice)	L	9.5-yr follow-up, incidence of CHD in relation to activity index	Increase of risk at highest intensity seen only in hypertensives (>160 mm Hg syst or >90 mm Hg diast or antihypertensive treatment)
Slattery et al. (229)	2548 M (U.S. Railroad Study)	L	17 to 20-yr follow-up of CVD and Total deaths	Relative to leisure expenditure of 15.2 MJ · wk^{-1}, 5.7 MJ · wk^{-1} 1.05, 1.04; 2.3 MJ · wk^{-1} 1.11, 1.08; 17 MJ · wk^{-1} 1.28, 1.21 (all adjusted for age, BP, cholesterol, and smoking); Relative to sedentary individuals, RR 0.75, activity <6 METs, RR 0.95 activity >6 METs,
Garcia-Palmieri et al. (77)	8793 M aged 45–64 yr (Puerto-Rican Heart Study)	L	8-yr follow-up; incidence of CVD	Inverse association to physical activity index for both total and hardest physical activity
Lakka et al. (126)	1453 M aged 42–60 yr	L	5-yr follow-up; incidence of myocardial infarction	Walking or cycling to work (4 METs) no influence on risk; relative to <0.7 h · wk^{-1} conditioning activity (6 METs); 0.7–2.2 h · wk^{-1}, RR 1.19; >2.2 h · wk^{-1}, RR 0.34
Rosengren and Wilhelmsen (195)	7142 M aged 47–55 yr, excluded if history of CHD or positive Rose questionnaire (Goteborg Study)	L	20-yr follow-up of total and CVD mortality	All-cause deaths relative to sedentary; moderate activity, regular exercise/training RR 0.75, 0.49 (BMI <24.1 kg · m^{-2}), RR 0.78, 0.54 (BMI 24.1–26.6 kg · m^{-2}), RR 0.77, 0.68 (BMI > 26.6 kg · m^{-2}) (all data adjusted for age) Cardiovascular deaths; moderate activity and regular exercise/training RR 1.09, 0.65, BMI <24.1 kg · m^{-2}); 0.61, 0.50 (BMI 24.1–26.6 kg · m^{-2}); 0.72, 0.58
Manson et al. (143)	72,488 F aged 40–65 yr, free of CVD or cancer	L	8-yr follow-up, fatal or nonfatal CHD	Similar reduction in risk for walking 3 h · wk^{-1} at brisk pace (RR 0.65, excluding those who engage in moderate-hard ("vigorous") exercise) and for moderate-hard ("vigorous") exercise >6 MET >4 h · wk^{-1}, RR 0.69, 0.63 if >7 h · wk^{-1}) (data adjusted for age, smoking, BMI, menopausal status, HRT, parental history of MI, vitamin supplements, alcohol, hypertension, diabetes, cholesterol, aspirin use)
Bijnen et al. (18)	472 M aged 65–85 yr (Zutphen Study)	L	5-yr follow-up, all-cause mortality	Mortality inversely related to minutes of physical activity/wk, but unrelated to intensity (hard ("heavy") vs light ("nonheavy") or type of activity. Data covaried for age, chronic disease, functional status, lifestyle factors
Effects of volume of physical activity				
Kannel and Sorlie (114)	1909 M, 2311 F aged 35–64 yr (Framingham Study)	L	14-yr follow-up of fatal and nonfatal CVD, simple activity index	Inverse association with volume of activity index (M only, after multivariate adjustment for confounders)
Kannel et al. (113)	1166 M aged 45–64 yr (Framingham Study)	L	24-yr follow-up fatal CVD, hours per day at activity-specific intensity	Age-adjusted risk relative to high physical activity index: moderate activity 1.30, low activity 1.62; inverse association persists after multivariate analysis
Sherman et al. (223)	1404 F 50–74 yr (Framingham Study)	L	16-yr follow-up CVD incidence and deaths	No association over quartiles of physical activity index
Paffenbarger et al. (176,173)	16,936 M 35–74 yr, no CHD at baseline (Harvard Alumni)	L	16-yr follow-up of CVD deaths	Risk relative to volume of 8.4 MJ · wk^{-1}: 1.28 for 2.1–8.4 MJ · wk^{-1}, 1.84 if <2.1 MJ · wk^{-1} (data adjusted for age)
Paffenbarger et al. (172)	11,864 M 45–84 yr (Harvard Alumni)	L	9-yr follow-up; total mortality vs various measures of activity	Relative to walking <5 km · wk^{-1}; 5–14 km · wk^{-1}, RR 0.78; >14 km · wk^{-1}, RR 0.67; Relative to climbing <20 floors · wk^{-1}; 20–54, RR 0.79; >54, RR 0.75. Relative to no sports play; Light (<4.5 METs), RR 1.10; moderate (>4.5 METs) 0.63; Relative to <1 h · wk^{-1} of moderate sports; 1–2 h · wk^{-1}, RR 0.63; >3 h · wk^{-1}, RR 0.47 (all data adjusted for age)
Paffenbarger et al. (172)	11,864 M 45–84 yr (Harvard Alumni)	L	9-yr follow-up; total mortality vs *change* in activity	Relative to consistent no sport; became inactive, RR 1.23; adopted sport, RR 0.71; remained moderate sport participant, RR 0.69 (all data adjusted for age, other components of activity, smoking, hypertension, BMI, and parental mortality before age 65 yr)
Linsted et al. (139)	9484 M >30 yr (Seventh-Day Adventists)	L	26-yr follow-up of CVD deaths, single activity question	Risk relative to inactive: moderate activity score 0.79, high activity score 1.02. Data adjusted for attained age. No significance after adjusting for SES, BMI and diet. Trend for high activity to *increase* mortality in those >80 yr
Villeneuve et al. (256) Arraiz et al. (11)	6246 M, 8196 F, 20–69 yr (Canada Health Survey)	L	7-yr follow-up of total deaths physical activity index (kJ · kg^{-1})	20–30% difference in RR with kcal · kg^{-1} · d^{-1} not statistically significant RR if participate in one vigorous activity 0.72 (0.53–0.96)
LaCroix et al. (125)	1645 M and F >65 yr	L	CVD hospitalizations and deaths	Relative to sedentary; RR walking 1–4 h · wk^{-1} 0.90, RR walking >4 h · wk^{-1} 0.73
Kushi et al. (124)	40,417 F aged 55–69 yr Free of cancer, CVD, no death in first 3 yr	L	7-yr follow-up total mortality	RRs similar for moderate physical activity (0.76, 0.70, 0.62) and vigorous activity (RRs 0.89, 0.74, 0.57). Benefit from moderate activity only once per week RR 0.78)
Sobolski et al. (234)	2363 M aged 40–55 yr (Belgian Fitness Study)	L	5-yr follow-up, incidence of death, fatal, and nonfatal CVD	Association with fitness, but not with 4-level classification of leisure or occupational activity (? adequate number of subject-years)

TABLE 2. *Continued*

Leon et al. (136)	12,138 M 35–57 yr (MRFIT Trial)	L	10.5-yr follow-up CVD mortality	Relative to 0–29 min · d^{-1} of leisure activity, 30–69 min · d^{-1} RR 0.81, >70 min · d^{-1}, RR 0.89. (data adjusted for age, smoking, cholesterol, diastolic BP) (BMI >26.6 kg · m^{-2})
Leon et al. (137)	12,138 middle-aged M	L	16-yr follow-up	Sample showed mainly light or moderate intensity activity; 10–36 min · d^{-1} associated with 29% and 22% reduction in risk of coronary heart disease and all-cause deaths
Hakim et al. (89)	707 M nonsmokers aged 61–81	L	12-yr follow-up	Risk of death 0.59 if walking >3.2 km · d^{-1} vs <1.6 km · d^{-1}. Benefit persists after adjusting for other risk factors
Haapanen et al. (87)	1072 M aged 35–63 yr	L	10-yr follow-up all-cause and CVD mortality 8.8 vs 3.3 MJ · wk^{-1}	Relative risk of all-cause mortality 0.36, CVD mortality 0.28 for 8.8 MJ · wk^{-1}
Weller and Corey (263)	6620 F >30 yr (Canada Fitness Survey)	L	7-yr follow-up, least vs most active	Data adjusted for age, disease or symptoms, smoking, marital, and employment status Odds ratio for cardiovascular mortality 0.51 (0.61 for fatal myocardial infarct)
Changes in atherosclerotic lesions				
Hambrecht et al. (91)	90 cases of stable angina	L	1-yr regression of atherosclerotic lesions at angiography with exercise program including cycle ergometry at 75% max capacity	Regression if expenditure >8.4 MJ · wk^{-1}, stable at 6.3 MJ · wk, progress if <4.2 MJ · wk^{-1}
Changes in clotting mechanisms				
Molz et al. (156)	10 untrained M, 10 F	L	30-min aerobic exercise, followed by brief maximal effort	Much larger increase of tissue plasminogen activator activity with brief maximal effort than with 30 min aerobic exercise
Szymanski and Pate (240)	12 active M aged 35 yr	X-over	50% vs 80% $\dot{V}O_{2max}$	Higher intensity gives greater increase of tissue plasminogen activator
Weiss et al. (262)	12 M aged 24 yr	X-over	Treadmill running for 1 h at 68 or 83% $\dot{V}O_{2max}$	Moderate exercise increased plasmin formation but not generation of thrombin or fibrin. Heavy exercise increased thrombin and fibrin but countered by larger formation of plasmin
Siscovick et al. (226)	2274 M and F >65 yr (Cardiovascular Health Study)	X-section	2-wk reported exercise intensity (light ("low", moderate, or hard ("high"))	Inverse association with serum fibrinogen, not greatly modified by adjusting for total energy expenditure
Urhausen et al. (254)	14 endurance-trained M	X-over	45 min at 85, 95, 100, or 105% of individual anaerobic threshold	Free plasma catecholamines increased disproportionately with intensity
Wang et al. (259)	10 sedentary, 10 active young M	X-over	cycle ergometer exercise hard vs moderate	Platelet adhesiveness and aggregation increased with hard exercise, suppressed by moderate exercise

L, longitudinal survey; X-over, cross-over trial; X-section, cross-sectional comparison.

to distinguish clearly between acute and chronic reductions in blood pressure.

Conclusions. The acute, exercise-induced reduction of blood pressure seems independent of the relative intensity of exercise (Category B Evidence), but the chronic response may be greater for moderate than for hard effort (Category B Evidence). The optimal intensity of effort for the prevention of stroke remains unclear.

PHYSICAL ACTIVITY AND METABOLIC HEALTH

The impact of physical activity on metabolic health occurs through a combination of the acute and chronic effects of exercise. The acute metabolic effects of a given bout of exercise may be enhanced if physical condition is improved (93).

Acute stimulation of metabolism. Ten small trials (nine with a crossover design, one randomized) have examined the acute effect of exercise upon resting metabolism (Table 4). Five of the 10 trials (33,182,203,224,248) controlled relative intensity of effort for the total volume of activity. Six trials found an intensity-related increase in the amount (33,182,224,248) or the duration (13,231) of the excess postexercise oxygen consumption for both leg- and arm-cranking exercise, with intensity being more important than the duration of activity (224). The timing of observations postexercise may influence the observed response (182); three other reports (one with control of total volume (203)) found no effect of intensity (80,203,204), and one noted that 3 h postexercise the response to activity at 50% of $\dot{V}O_{2max}$ was greater than that at 70% $\dot{V}O_{2max}$ (39).

Fat loss. Traditionally, the total volume of physical activity has been held to be more important than the intensity of effort in achieving a significant decrease in body fat content. However, hard exercise could facilitate the process by increasing resting energy expenditure (127,247) or lean body mass (and thus the ability to undertake endurance exercise (106)). Hard effort might also be helpful in reaching the requisite total weekly energy expenditure (53,108).

Eight small-scale randomized trials and four larger cross-sectional studies have examined the impact of differing programs on changes in body composition; the total volume of physical activity was controlled in only two studies (56,84). Two reports compared structured with lifestyle activities, hard intensity activity being less in the lifestyle program (10,59). Fat loss was similar for the two groups, but in one of these comparisons, the lifestyle group lost more lean body mass (10), a point confirmed in another trial (84). Two further trials (56,200) found no significant changes in body mass relative to control at any of two or three intensities of effort. One study found reductions in skin-fold thicknesses with both resistance and aerobic exercise (42). The remaining reports disagreed as to whether the response was unchanged (72,84) or increased (35,54,104,108,246) by an increase in the relative intensity of exercise; however, total volume of physical activity was controlled in one of the two negative reports (84).

TABLE 3. Physical activity in the control of hypertension or stroke.

Author	Sample	Design	Program	Response
Acute reductions in blood pressure				
Macdonald et al. (141)	10 aged 35.0 yr	X-over	Exercise at 50% or 75% $\dot{V}O_{2max}$	Similar reductions of BP for 60 min postexercise
Marceau et al. (146)	10 M, 1 F hypertensives	X-over	Exercise at 50% or 70% $\dot{V}O_{2max}$	Equal decrease of 24-h blood pressure (5 mm Hg) in two groups but harder intensity has less effect on daytime pressures
Forjaz et al. (69)	12 young normotensive, 12 control	X-over	Cycle ergometry at 30, 50, or 80% $\dot{V}O_{2peak}$ for 45 min	Decrease in syst and diast BP similar for 3 intensities
Williams (265)	7059 M, 1837 F runners	X-section	Running distance or velocity vs BP	Velocity had greater effect than distance; syst BP (13.3×, M; 5.7× F), diast BP (2.8×, M)
Chronic reductions in blood pressure				
Hagberg et al. (88)	33 hypertensives	Lr	9 months exercise at 53% or 73% $\dot{V}O_{2max}$ vs control	Decrease of diast 11–12 mm Hg in both exp groups; decrease of syst 20 mm Hg (moderate) vs 8 mm Hg hard intensity
Matsusaki et al. (148)	26 mild hypertensives	Lr	10 wk of exercise at 50% or 75% $\dot{V}O_{2max}$	Significant decreases moderate exercise (9/6 mm Hg); changes smaller (3/5 mm Hg) and nonsignificant at harder intensity
Rogers et al. (192)	18 borderline hypertensives	Lr	40–50 or 70–80% $\dot{V}O_{2max}$ vs control, 12 wk exercise, 3/wk	Light intensity exercise reduced resting BP and syst and diast pressure responses to Stroop test. Moderate intensity only reduced diast pressure response to Stroop test
Braith et al. (31)	44 sedentary subjects 60–79 yr	Lr	6 months progressing to 70% HRR, 45 min/session or 85% HRR, 35 min vs control	8–9 mm Hg decrease of syst BP in both exercise groups
Cox et al. (47)	126 F aged 40–65 yr	Lr	12 months, 40–55% or 65–80% HRR, home- or center-based programs	2.7 mm Hg fall of BP at 6 months but not 12 months moderate but not hard intensity program
Dunn et al. (59)	116 M, 119 F aged 35–60 yr	Lr	Lifestyle activities 30 min most days vs structured activity program at 50–85% $\dot{V}O_{2max}$	Equal decrease of blood pressure (3/5 mm Hg) in two groups
Duncan et al. (56)	46 F aged 20–40 yr	Lr	24 wk at 56%, 67% or 86% HRmax	No impact on BP at lowest intensity. Dose controlled for distance walked
Kingwell and Jennings (121)	7 M, 7 F (normotensive)	X-over	4 week bouts of walking at 50% $\dot{V}O_{2max}$ (60 min, 5/wk), cycle ergometry at 65–70% Wmax (30 min, 3/wk) or 80–90% Wmax (15 min, 5/wk) vs control	Largest decrease of BP (5/3 mm Hg) with moderate cycling Pressure also reduced by walking but not by hard exercise intensity
Cononie et al. (121)	49 M and F aged 70–79 yr	Lr	6-month program of resistance training vs endurance at 75–85% $\dot{V}O_{2max}$ vs control group	BP reduced 5/4 mm Hg by endurance exercise. No change with resistance exercise
Tashiro et al. (241)	10 mild hypertensives	X-over	10-wk cycle ergometry at 50 or 75% $\dot{V}O_{2max}$	No significant effect of intensity
Folsom et al. (68)	41,837 F aged 55–69 yr	L	2 yr follow up for hypertension	RR of hypertension 30% lower if hard intensity activity, 10% lower if moderate vs light intensity
Paffenbarger et al. (177)	14,998 M	L	Followed in middle age for 6–10 yr	RR of hypertension 1.30 if energy expended <8 MJ · wk^{-1}
Haapanen et al. (86)	1340 M, 1500 F aged 35–63 yr	L	10-yr follow-up for hypertension	Incidence inversely associated with total activity and with hard physical activity >1/wk in men
Moreira et al. (157)	28 sedentary hypertensives	Lr	10 wk at 20% or 60% max power output on cycle ergometer	Similar decrease of syst and diast BP at two intensities
Roman et al. (193)	30 F, chronic hypertensives	L	3 + 12 months at 70% max HR, vs subsequent 12 months at >70% max HR	No significant additional decrease in BP at higher intensity
Prevention of stroke				
Paffenbarger et al. (173)	16,936 M 35–74 yr	L	Followed for 16 yr, death from stroke	Relative to 8.4 MJ · wk^{-1}, 1.2–8.4 MJ · wk^{-1}, RR 1.25; <1.2 MJ · wk^{-1}, RR 2.71 Differences persist after adjusting for age, smoking, and hypertension
Wannamethee and Shaper (260)	7630 M aged 45–59 yr	L	8.5-yr follow-up stroke incidence relative to activity index	Relative to inactive, RR occasional 0.7, light 0.5, moderate 0.4, moderately hard ("vigorous") 0.3, vigorous 0.2 (all age adjusted)
Linsted et al. (139)	9484 M >30 yr	L	26-yr follow-up; fatal stroke	Relative to low activity; moderate activity, RR 0.78; high activity, RR 1.08 (data adjusted for SES, BMI, diet)
Kiely et al. (118)	1897 M 35–69 yr; 2299 F 35–68 yr; M 49–83 yr; F 49–83 yr	L	follow-up 32, 18 yr; fatal or nonfatal cerebral episode	Relative to low activity; cohort I, medium, RR 0.90, high, 0.84; cohort II, medium, 1.21, high 0.89; cohort III, medium 0.41, high 0.53; cohort IV, medium 0.97, high 1.21. Overall, benefit no greater for high than for moderate physical activity (data controlled for many potential confounders)
Menotti and Seccareccia (151)	99,029 M 40–59 yr	L	follow-up for 5 yr, fatal stroke	U-shaped association; incidence lowest for moderate physical activity
Herman et al. (101)	132 stroke patients, 239 age- and sex-matched controls aged 40–74 yr	Cc	Assessment of lifetime leisure activity (little to regular–heavy)	Relative to small amount; moderate, RR 0.72; large, RR 0.41 (adjusted for various potential confounders)
Sacco et al. (196)	369 cases, 678 controls aged 70 yr	Cc	Activity over 2 wk (prospective)	Dose-response for intensity (light/moderate OR = 0.42) and duration

Lr, longitudinal controlled study with randomized assignment; L, longitudinal study; Cc, case control; RR, relative risk; SES, socioeconomic status; BMI, body mass index; HRR, heart rate reserve.

TABLE 4. Physical activity and metabolic health.

Author	Sample	Design	Program	Response
Acute stimulation of metabolism				
Phelain et al. (182)	8 active F aged 22–31 yr	X-over	50% vs 75% $\dot{V}O_{2max}$, 2.1 MJ total	Greater EPOC with hard intensity
Smith et al. (231)	8 trained M, 8 F	X-over	40, 50, or 70% of $\dot{V}O_{2max}$	Duration of excess postexercise oxygen consumption (EPOC) Increased with exercise intensity
Short et al. (224)	5 M, 5 F aged 27 yr	X-over	Arm crank at 35% $\dot{V}O_{2max}$ for 15 or 30 min vs 70% $\dot{V}O_{2max}$ for 15 min	Excess postexercise oxygen consumption affected more by intensity than duration of effort (EPOC 33 vs 12 or 10 kJ)
Treuth et al. (248)	8 F aged 28 yr	X-over	60-min cycle ergometry at 50% $\dot{V}O_{2max}$ vs 60-min 2/2 interval work at 100% $\dot{V}O_{2max}$	High-intensity effort elicited larger energy expenditure at rest, exercise and over 24-h period
Segal et al. (204)	10 lean, 10 obese M	X-over	1 h of cycling at 50 or 100 W	Both intensities of effort enhance thermal effect of food in obese but not in lean individuals
Sedlock et al. (203)	7 mod. active young F	X-over	850 kJ cycling at 40 or 60% $\dot{V}O_{2max}$	Excess postexercise oxygen consumption did not differ with intensity
Bahr and Sejersted (13)	6 healthy M	X-over	80 min at 29, 50 or 75% $\dot{V}O_{2max}$ vs control	No EPOC at 29%, EPOC for 3.3 h at 50%, 10.5 h at 75% $\dot{V}O_{2max}$
Chad and Quigley (39)	5 trained, 5 untrained F	X-over	30-min cycle ergometry at 50 or 70% $\dot{V}O_{2max}$	3 h post-ex, larger increase of EPOC at 50% than at 70% $\dot{V}O_{2max}$ Associated greater estimated fatty acid oxidation
Broeder et al. (33)	5 lean, 5 borderline obese (20–25% fat)	X-over	3 MJ on treadmill at 30 or 60% $\dot{V}O_{2max}$	EPOC for 3 h postexercise if given noncaloric fluid +13.5% at 60% $\dot{V}O_{2max}$, +5.5% at 30% $\dot{V}O_{2max}$
Goben et al. (80)	16 lean M	R	30-min high- or low-intensity exercise	Total metabolic expense for 3 h postmeal similar after high and low intensity
Fat loss				
Duncan et al. (56)	59 F aged 20–40 yr (low risk lipid profile)	Lr	24-wk walking at 8, 6.4, or 4.8 km · h^{-1} vs controls (56, 67, or 86% Wmax)	No significant differences in weight change relative to control; walking distance controlled
Dunn et al. (59)	116 M, 119 F aged 35–60 yr	Lr	2-yr lifestyle activities 30 min most days vs structured program at 50–85% $\dot{V}O_{2max}$	2.4% decrease of fat in lifestyle group; 1.9% in structured group
Andersen et al. (10)	38 obese F aged 43 yr	Lr	16-wk study, aerobic vs lifestyle activity plus dieting	Weight loss 8.3, 7.9 kg; but lifestyle group lost more lean mass
Grediagin et al. (84)	12 moderately fat F	Lr	1.25 MJ/session, 4 times/wk for 12 wk at 50% or 80% of $\dot{V}O_{2max}$	Each group lost 2.3 kg fat; hard-intensity group gained more lean body mass
Bryner et al. (35)	15 unfit F aged 18–34 yr	Lr	11 wk exercise at 132 or 163 beats · min^{-1} 40–45 min/session, 4/wk	5% decrease of body fat with hard, no change with moderate intensity
Jeffery et al. (108)	193 obese men and women	Lr	Randomized to 5 treatments, 18-month follow-up	Largest weight loss in those with greatest energy expenditure at 18 months (10.7 MJ · wk^{-1}, of which 3.3 MJ · wk^{-1} hard intensity)
Santiago et al. (200)	25 sedentary women age 30 yr	Lr	Randomized to walk at 52% $\dot{V}O_{2max}$ jog at 79% $\dot{V}O_{2max}$ or control for 20 wk 4 times/wk, 4.8-km distance	No significant change of body mass in any group
Cononie et al. (42)	49 M and F aged 70–79 yr	Lr	6-month program of resistance training vs endurance at 75–85% $\dot{V}O_{2max}$ vs control group	Both groups showed reductions in skinfold thicknesses
French et al. (72)	1639 M, 1913 F	X-sect, L	2-yr follow-up of weight-loss program	Initially, hard-intensity activity negatively correlated with body mass. Loss of mass over 2 yr associated with either walking or high-intensity activity
Hopkins et al. (104)	140 randomly selected adults	X-sect	Activity questionnaire vs skinfolds	"Hard" physical activity negatively correlated with skinfold readings
Tremblay et al. (246)	1366 F, 1257 M	X-sect	Activity questionnaire vs skinfolds and waist/hip ratios	Hard ("vigorous") physical activity associated with lower skinfolds and waist/hip ratios
DiPietro et al. (54)	6125 M, 12,557 F >18 yr	X-sect	Activity questionnaire vs BMI	Prevalence of BMI >30 kg · m^{-2} negatively related to intensity of activity; walking also associated with lower BMI, but only if age >40 yr
Acute changes in lipid metabolism				
Crouse et al. (49)	39 hypercholesterolemic M	Lr	80% vs 50% $\dot{V}O_{2max}$	Lipids and apoliprotein concentrations postexercise not influenced by exercise intensity
Pronk et al. (187)	11 F aged 34 yr, 10 F aged 55 yr	X-over	Treadmill walking to expend 1.5 MJ at 50% or 70% $\dot{V}O_{2max}$ (no controls)	Significant effect of relative intensity in premenopausal F for total and LDL-cholesterol
Gordon et al. (82)	12 M recreational runners	X-over	3.35 MJ treadmill energy expended at 60% or 75% $\dot{V}O_{2max}$	Increase in HDL-cholesterol at hard intensity only
Davis et al. (51)	10 well-trained runners	X-over	Treadmill run, 60 min at 75% $\dot{V}O_{2max}$ or 90 min at 50% $\dot{V}O_{2max}$	Neither intensity modified plasma lipids, lipoproteins, or apolipoproteins Unchanged by 10 wk training (75% $\dot{V}O_{2max}$, 10 wk, 5/wk)
Friedlander et al. (75)	40 M aged 26 yr	X-over	Cycle ergometer at 45 or 65% $\dot{V}O_{2max}$	Plasma FFA kinetics inversely related to exercise intensity
Friedlander et al. (73)	8 F aged 24 yr	X-over	Cycle ergometer at 45 or 65% $\dot{V}O_{2max}$	Plasma FFA kinetics similar at two intensities of exercise
Tsetsonis and Hardman (249)	5 M, 4 F normolipidemic, 28 yr	X-over	Walk 3 h at low vs 1.5 h at moderate intensity vs control	Postprandial lipemia did not differ between walking trials
Chronic effects on lipid profile				
Duncan et al. (56)	59 F aged 20–40 yr (low risk lipid profile)	Lr	24-wk walking at 8, 6.4, or 4.8 km · h^{-1} vs controls	No significant intergroup differences in lipid profile relative to control; data controlled for walking distance
King et al. (119)	197 M, 160 F aged 50–65 yr	Lr	Hard intensity group (73–88% peak HR) vs hard ("high") or light ("low") intensity; home vs control for 1 yr	No significant intergroup differences in lipids
King et al. (120)	149 M, 120 F aged 50–65 yr	Lr	2-yr follow-up of previous study	Significant increase in HDL-cholesterol in home-based programs, especially low intensity (60–73% peak HR)
Santiago et al. (200)	25 sedentary women aged 30 yr	Lr	Randomized to walk at 52% $\dot{V}O_{2max}$ jog at 79% $\dot{V}O_{2max}$ or control for 20 wk 4 times/wk, 4.8-km distance	No significant change of lipid profile in any group; data controlled for distance

TABLE 4. *Continued*

Dunn et al. (59)	116 M, 119 F overweight M & F aged 35–60	Lr	Two year comparison of 30 min lifestyle activity most days vs structured programme at 50–85% $\dot{V}O_{2max}$	No significant change in cholesterol; triglycerides increased in structured but not in lifestyle group
Crouse et al. (48)	26 hypercholesterolemic M, aged 47 yr	Lr	24 wk of cycle ergometry, 1.5 MJ/session, 3/wk at 50 or 80% $\dot{V}O_{2max}$	82% increase in HDL-cholesterol, independent of relative intensity of activity
Andersen et al. (10)	38 obese females aged 43 yr	Lr	16-wk study, aerobic vs lifestyle activity plus dieting	16% reduction of triglycerides, 10% reduction of cholesterol, did not differ between groups
Spate-Douglas and Keyser (235)	25 healthy F	Lr	12 wk, 3.2 km walk 3/wk at 60 or 80% HRR	Increase in total and HDL-2-cholesterol marginally less with hard than with moderate intensity walking; data controlled for distance
Ohta et al. (169)	65 M 297 F obese aged 47 yr	L	5-month walking + diet restriction	Correlation between daily walking distance and increase in HDL-cholesterol
Mensink et al. (153)	5943 M, 6039 F aged 25–69 yr	X-section	High (7.5–9.0 METs), moderate (3.0–4.5 or 5.0–7.0 MET)	HDL-cholesterol, HDL/total cholesterol, triglycerides associated with hard-intensity activity (M only); moderate activity associated with HDL-cholesterol (M), HDL/total, triglycerides (F)
Tucker and Friedman (251)	3621 adults aged 40 yr	X-section	Walking duration vs Total/HDL-cholesterol	Risk of elevated total/HDL relative to no weekly walking: 0.5–2 h = 1.11, 2.5–4 h 0.48, 4.5 h + 0.46 (data controlled for age, gender, SES, fat, alcohol, smoking, other exercise)
Williams (264)	1837 F recreational runners	X-section	Lipids vs running distance	HDL-cholesterol increased by 0.003 mmol · L^{-1} per km · wk^{-1} running
Williams (265)	7059 M, 1837 F runners	X-section	Running distance or velocity vs lipids	Running distance 6× more effect than velocity in both sexes
Cook et al. (43)	35 M postal carriers aged 47 yr	X-section	Physical activity score vs lipids	Large-scale integrated activity monitor score correlated with total HDL-cholesterol and HDL_2 subfraction; HDL_2 also correlated with distance walked on the job
Wood et al. (266)	48 M aged 30–55 yr screened for diseases, body mass, lipids	X-section	Lipids vs running distance	Distance run per wk correlated with HDL-cholesterol, and inversely correlated with total and LDL-cholesterol, apolipoprotein B
Blood glucose regulation				
Smutok et al. (233)	26 untrained M aged 54 yr NIDDM or impaired glucose tolerance	Lr	20-wk treadmill walk vs strength training vs control	Area under glucose tolerance curve improved equally by walk and strength programs
Kang et al. (112)	6 M NIDDM, 6 matched control	X-over	Cycle ergometry at 50 or 70% $\dot{V}O_{2peak}$ (duration matched for energy expended)	Increase in glucose utilization similar for two intensities of effort
Kang et al. (112)	6 obese M, 6 obese M with NIDDM	X-over	7-d programs, 70% $\dot{V}O_{2max}$ × 50 min vs 50% × 70 min	Improvement of insulin sensitivity at 70%, but not at 50% $\dot{V}O_{2max}$
Schwarz et al. (202)	10 M aged 28 yr	X-over	10 min of low- or high-intensity exercise	Increases in insulin-like growth factors and binding protein substantially greater with hardintensity exercise
Cooper et al. (44)	7 M 23–34 yr	X-over	Glucose uptake at rest vs 40% or 80% $\dot{V}O_{2max}$	Light intensity gives no significant increase of glucose uptake; more than doubled with hard-intensity exercise.
Romijn et al. (194)	5 trained subjects	X-over	Glucose uptake and fatty acid release at 25, 65, 85% $\dot{V}O_{2max}$	Glucose uptake increases with exercise intensity, but fatty acid release greatest at light intensity of effort
Braun et al. (32)	8 F with NIDDDM	X-over	Glucose uptake at 50% or 75% $\dot{V}O_{2max}$ vs control, equal energy expenditure	Light intensity as effective as hard intensity in augmenting glucose usage
Friedlander et al. (74)	17 healthy F aged 24 yr	X-over	45 or 65% $\dot{V}O_{2peak}$	Rates of glucose appearance, disappearance and oxidation all higher at 65 than at 45% $\dot{V}O_{2max}$
Young et al. (268)	7 trained, 7 untrained M	X-over	Insulin response to glucose load 14 h after 40 min at 40% or 80% $\dot{V}O_{2max}$	In untrained subjects, 40% decrease in insulin response after either exercise bout
Ben-Ezra et al. (14)	24 untrained F aged 23 yr	X-over	40% $\dot{V}O_{2max}$, 87 min vs 70% $\dot{V}O_{2max}$ 50 min vs control	Hard but not light intensity reduces area under insulin curve
Raguso et al. (189)	7 M with IDDM, controls matched for age, wt, $\dot{V}O_{2max}$	X-section	Exercise at 45% vs 75% $\dot{V}O_{2max}$	IDDM metabolizes less carbohydrate than controls at 45% but not at 75% $\dot{V}O_{2max}$
Mayer-Davis et al. (149)	1467 M and F aged 40–69 yr (normal to mild diabetes mellitus)	X-section	Vigorous (>6 METs) and nonvigorous (<6 METs) activity	Each positively and independently associated with insulin sensitivity after control for confounders
Prevention of maturity-onset diabetes mellitus				
Helmrich et al. (100)	5990 M, aged 45–64 yr free of diabetes at entry	L	14-yr follow-up, incidence of diabetes mellitus	6% decrease in incidence for each 2.1 MJ · wk^{-1} expended in walking, stairs, and sports (data adjusted for age, BMI, hypertension, parental history of diabetes)
Manson et al. (145)	87,253 F aged 34–59 yr free of diabetes, CVD and cancer at entry	L	8-yr follow-up incidence of diabetes	Relative to hard ("vigorous") exercise (enough to develop sweat) <1/wk; >1/wk, RR 0.84 (data standardized for age, BMI, family history, smoking, alcohol, hypertension, cholesterol, family history of CHD)
Manson et al. (144)	21,271 M aged 40–84 yr free of diabetes, CVD stroke, or cancer at entry	L	5-yr follow-up incidence of diabetes	Relative to hard ("vigorous") exercise (enough to develop sweat) <1/wk; >1/wk, RR 0.70 (data standardized for age, BMI, smoking, alcohol, blood pressure, hypertension history, cholesterol, parental history of myocardial infarction)
Burchfiel et al. (36)	6815 M aged 45–68 yr	L	6-yr follow-up for diabetes Activity index (intensity × time)	Relative to lowest quintile; progressive reduction of RR to 0.46 (0.40 in those
	Free of diabetes at entry	Activity index (intensity × time)		
Haapanen et al. (86)	1340 M, 1500 F, aged 35–63 yr	L	10-yr follow up	In women, incidence of diabetes related to total weekly activity and weekly vigorous activity
	1340 M, 1500 F, aged 35–63 yr	L	10-yr follow up	In women, incidence of diabetes related to total weekly activity and weekly hard physical activity

Lr, longitudinal randomized controlled trial; L, longitudinal study; R, randomized trial; X-over, crossover trial; X-section, cross-sectional comparison; RR, relative risk; BMI, body mass index; CVD, cardiovascular disease; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; FFA, free fatty acids; EPOC, excess postexercise oxygen consumption.

TABLE 5. Physical activity and prevention of osteoporosis.

Author	Sample	Design	Program	Response
Hatori et al. (97)	35 F aged 45–67 yr	Lr	7-month follow-up, exercise above or below anaerobic threshold vs control; no hormones, normal diet	1.1% increase above anaerobic threshold, vs 1.0% decrease below threshold vs −1.7% in controls
Pruitt et al. (188)	26 F aged 65–79 yr	Lr	80% 1 RM vs 40% 1 RM with twice number of repetitions vs control 3 $d \cdot wk^{-1}$ for 1 yr	Similar (NS) increases in lumbar and total hip bone mineral density in hard and light intensity groups
Krall and Dawson-Hughes (122)	239 F aged 43–72 yr	X-section	Weekly walking distance vs bone density; vit D supplements	Legs, trunk and whole body but not arms show greater bone density if walk 12 $km \cdot wk^{-1}$ vs <1.6 $km \cdot wk^{-1}$; benefit less for intermediate distances
Coupland et al. (46)	580 F aged 45–61 yr	X-section	Walking pace, duration, frequency vs bone mineral density at selected sites	Trochanter density 8% greater for steady and fairly brisk than for slow-paced walking; also related to volume of stair climbing/day

Lr, longitudinal randomized controlled trial; X-section, cross-sectional study.

Lipid metabolism. One small randomized trial and six small-scale crossover trials examined acute changes in lipid metabolism; five (49,51,82,187,249) controlled for total volume of physical activity. Postprandial lipemia did not differ with relative exercise intensity (249). In men (but not in women), the effect on plasma free fatty acid kinetics was greater with a harder relative intensity of activity (73,74), uncontrolled for total volume. One trial found no acute changes in the lipid profile (51), but in the remaining two studies of plasma lipids, changes showed a significant effect of relative intensity (82,187).

Chronic changes in lipid profile have been examined in eight small-scale randomized longitudinal trials, and seven nonrandomized studies. Five studies controlled for the distance walked (48,56,200,235,265). Four of the randomized trials found little or no change in lipid profile relative to control at any of two or three relative intensities of effort (56,59,119,200). Two other reports found greater benefit from moderate than from hard intensity programs (120,235), and in the remaining two studies, there was evidence of benefit but no effect of relative intensity (10,48). The majority of the cross-sectional studies demonstrated an effect of exercise volume rather than intensity. The report of Williams (265) specifically noted that the effect on lipid profile was 6 times larger for running distance than for running velocity.

Blood glucose regulation. Eight small crossover trials, one randomized trial, and two cross-sectional studies have examined the influence of exercise intensity on glucose utilization and/or insulin sensitivity. Trials have differed in their choice of subjects (trained, untrained, insulin-dependent, or nondependent diabetics). Three studies (14,32,112) controlled for the total volume of activity. Three of four trials (44,74,194) found a greater increase of glucose uptake at the higher intensity of effort. Two negative studies (32,233) involved patients with noninsulin dependent diabetes mellitus, and one of these equated energy expenditures across intensities. Two of three trials (14,112) but not (268) found an improvement of insulin sensitivity only at the harder intensity of effort.

Prevention of maturity-onset diabetes mellitus. Five large-scale studies have explored cross-sectional associations between physical activity and the incidence of maturity-onset diabetes mellitus. Two studies have pointed to the importance of activity sufficient to induce a sweat (144,145), and two others have pointed to progressive protection from an increased total volume of energy expenditure (86,100), but no one appears to have explored the absolute versus relative intensity issue systematically.

Conclusions. As with blood pressure, there has sometimes been a failure to distinguish between the acute and chronic metabolic effects of physical activity. Many of the metabolic benefits of physical activity such as a normalization of lipid profile seem to depend on the total volume rather than the intensity of exercise (Category B and Category C Evidence). However, the excess postexercise oxygen consumption seems to reflect the relative intensity of effort (Category B Evidence), and programs that enhance lean mass may increase the ability of overweight individuals to exercise.

OSTEOPOROSIS

The extent of weight-bearing and the application of resistive force are probably more important than either the relative or the absolute intensity of physical activity when seeking to prevent osteoporosis. Available information (Table 5) includes two small randomized controlled trials covering periods of 7 months (97) and 1 yr (188), and two larger cross-sectional studies (46,122), all performed on postmenopausal women. Hatori et al. (97) noted that lumbar vertebral bone mineral density was increased by 1.0% if the intensity of physical activity exceeded the individual's anaerobic threshold, whereas a lighter intensity was associated with a 1.0% loss, not significantly different from the 1.7% loss seen in control subjects (97). However, in the one study where the total work performed was equalized (188), benefit was similar from contractions at 40% and 80% of 1 RM. The cross-sectional observations suggest effects from the volume of activity and from the intensity (uncontrolled for volume).

Conclusions. There is some suggestion (Category B Evidence) that harder relative intensities of effort are more effective in augmenting bone density, but this may be due in part to an associated increase in the volume of physical activity.

PHYSICAL ACTIVITY AND OPTIMIZATION OF IMMUNE FUNCTION

A lymphocytosis develops at the immediate end of a bout of exercise, and a suppression of the immune response then persists for some hours. Six small-scale stud-

TABLE 6. Physical activity and the optimization of immune function.

Author	Sample	Design	Program	Response
Nieman et al. (165)	10 well-conditioned M aged 22 yr	X-over	45 min at 50% or 80% $\dot{V}O_{2max}$	Hard intensity gives greater post-ex lymphocytosis, and more marked lymphopenia and suppression of ConA proliferative response 1–3.5 h post-ex
Strasner et al. (238)	8 F	X-over	25-min cycle ergometry at 40 or 80% $\dot{V}O_{2max}$ vs control	Trend to suppression of NK activity 90 min postexercise at hard intensity of effort only
Tvede et al. (253)	6 healthy adults	X-over	60 min at 25, 50, or 75% $\dot{V}O_{2max}$	No changes with 25% intensity; greater with 75% than with 50% intensity. Decrease of CD16+ and CD56+ count and PHA-stimulated lymphocyte proliferation 2 h postexercise; suppression of NK and LAK activity decreased postexercise at 75% only
MacNeil et al. (142)	30 subjects at 3 fitness levels	X-over	30 min at 65% $\dot{V}O_{2max}$, 60 min at 30% $\dot{V}O_{2max}$, 60 min at 75% $\dot{V}O_{2max}$, and 120 min at 65% $\dot{V}O_{2max}$	Depression in mitogenesis 2 h postexercise in all fitness groups. Response not increased with longer duration of exercise. In high fitness group, trend to greater response at harder-intensity effort
Robson et al. (191)	18 M athletes aged 23 yr	X-over	Cycle ergometry (80% $\dot{V}O_{2max}$ for 1 h or 55% $\dot{V}O_{2max}$ for 3 h)	Similar reductions of *in vitro* neutrophil degranulation in response to bacterial lipopolysaccharide
McDowell et al. (150)	9, 9 M aged 24 yr	L	Series (1) 15, 30, or 45 min at 60% $\dot{V}O_{2max}$; series (2), 20 min at 50, 65, or 80% of $\dot{V}O_{2max}$	No regimen changed serum IgA for 2 h postexercise

ies have looked at the effects of various intensities of effort on immune function (Table 6); three of these studies (142,150,191) controlled for the total volume of physical activity. One of these three reports noted no change in serum IgA at any intensity of effort (150), but four of the five remaining studies (142,165,238,253) found that a hard relative intensity of effort (75–80% of $\dot{V}O_{2max}$) was needed to induce even a transient immunosuppression. The negative report considered primarily the *in vitro* neutrophil degranulation response to bacterial lipopolysaccharide (191).

Conclusions. There is good evidence (Category B) that a hard relative intensity of exercise is needed to cause even a transient suppression of circulating immune function.

Physical activity and cancer. In the case of cancer prevention, it is particularly important to maintain the specified pattern of physical activity for many years. Seven large-scale nonrandomized longitudinal studies (4,11,40,111,136,170,261) and a meta-analysis (222) have explored the effects of the dose of physical activity upon all-cancer death rates (Table 7); only one report commented on relative intensity (261), and this failed to standardize for total volume of energy expended. Individual reports show rather inconsistent effects. A meta-analysis found a greater benefit from a large rather than a moderate dose of physical activity (222), although the effects of intensity were not clearly distinguished from volume.

Of individual site cancers, research has focused particularly on the colon. Here, data are drawn from six nonrandomized longitudinal studies (79,131,134,206,245), three case-control studies (78,228,230), and the meta-analysis (222). Again, the issue of relative intensity is not resolved. The most convincing single study (230) used the case-control technique to show a much greater protection from hard than from light intensity activity, but a rather similar effect from small, moderate, and moderately large volume relative to a large volume of physical activity. These observations would be consistent with postulated benefit from an increased local synthesis of prostaglandin F_2, and thus a speeding of colon transit time (45). In contrast, a 16-yr follow-up of 53,242 men and 28,274 women found an adverse effect of regular training relative to a sedentary lifestyle in men (but not in women) (245). Further, in the meta-analysis (222), benefit was greater for light than for moderate activity.

One large study of female breast tumors found the greatest benefit from the largest volume of physical activity, although this was true only of postmenopausal women (205). The meta-analysis (222) showed little difference between light and moderate activity in the case of breast and female reproductive tract tumors, although in the case of prostate tumors the largest benefit was seen with light rather than moderate activity. Again, volume was not clearly distinguished from intensity in most of these studies.

Conclusions. Despite a substantial number of epidemiological studies (Category C Evidence), the issue of the relative intensity of effort needed for protection against various types of cancer remains unresolved and largely unexplored.

ENHANCEMENT OF MENTAL HEALTH

Fourteen studies (Table 8) have looked at the effects of exercise intensity upon mental health, eight considering acute and six chronic responses. Most are based on relatively small samples of subjects, and with two exceptions (147,207), the subjects have had only minor (nonclinical) disturbances of affect. Four of the acute trials found a larger effect at harder relative intensities of effort, but with one exception (65), the effect of a harder relative intensity was not distinguished from that of an increased volume of physical activity. With the exception of one study (167), the evidence on long-term decreases in anxiety suggests that a moderate relative intensity of exercise may be more effective than hard intensity effort. Indeed, one trial found an increase of anxiety with hard intensity training (116).

Conclusions. Further examination of the acute effects of relative exercise intensity on mental health is needed, controlling for the volume of physical activity that is undertaken. The chronic benefits of physical activity seem associated with a moderate rather than a hard relative intensity of effort (Category B Evidence).

TABLE 7. Physical activity and cancer prevention.

Author	Sample	Design	Program	Response
All cancers				
Albanes et al. (4)	5138 M, 7407 F	L	10-yr follow-up; cancer incidence vs activity index	Relative to very active. Moderate activity, RR 1.1 in M, 1.0 in F; inactive, 1.2 in M, 1.00 in F (data adjusted for age, smoking, SES, BMI, diet, reproductive and family history, race)
Arraiz et al. (11)	6246 M, 8196 F, aged 20–69 yr	L	7-yr follow-up; cancer incidence relative to energy expenditure (expressed in kcal · kg · wk^{-1})	Relative to very active. Active, RR 1.4; moderately active, RR 0.8; sedentary, RR 1.2. Clearer relationship to fitness level (data adjusted for age, sex, smoking, and alcohol consumption)
Chang-Claude and Frentzel-Beyme (40)	858 M. 1046 F	L	8-yr follow-up; cancer incidence relative to activity	Relative to hard ("high") activity. Moderate ("medium") activity, RR 1.00; light ("low") activity, RR 1.05 (data adjusted for BMI, smoking, meditation, diet)
Kampert et al. (111)	25,341 M, 7080 F	L	8-yr follow-up, cancer deaths relative to activity	Relative to sedentary. Very active, 0.15 (M), 2.86 (F); moderate activity, RR 0.41 (M), 0.95 (F); low activity 0.72 (M), 0.84 (F); effects more consistent for fitness level (data adjusted for age, smoking, chronic disease, ECG abnormalities, year of examination)
Leon et al. (136)	12,138 M	L	10.5-yr follow-up, cancer incidence relative to duration of moderate activity	Relative to >70 min · wk^{-1} moderate activity; 29–69 min, RR = 1.22; <29 min · wk^{-1}, 1.06 (data adjusted for age, diastolic BP, cholesterol, smoking)
Paffenbarger et al. (170)	16,936 M	L	10–16-yr follow-up, cancer incidence relative to weekly energy expenditure	Relative to 8.4 MJ · wk^{-1}; 2.1–8.4 MJ · wk^{-1}, RR 1.02; <2.1 MJ · wk^{-1}, RR 1.47 (adjusted for age, BMI, smoking)
Wannamethee et al. (261)	7735 M	L	9.5-yr follow-up, cancer mortality activity classification	Relative to inactive or occasional activity. Light/moderate, RR 0.84; moderate/hard, 0.59 (data adjusted for age, cholesterol, BMI and heart rate)
Shephard and Futcher (222)	Meta-analysis			Seven studies in men looked at exercise intensity/volume; variance-weighted geometric mean relative to hard intensity/volume; moderate, 1.23 1.66 (1.35–2.04) (1.00–1.51), low
Colon cancers				
Giovanucci et al. (79)	47,723 M, aged 40–75 yr	L	6 yr follow-up; colon cancer vs Activity in MET-h/wk	Relative to 46.8 MET-h · wk^{-1}; 22.6 MET-h · wk^{-1}, RR 1.47; 11.3 MET-h · wk^{-1}, RR 1.77; 4.8 MET-h · wk^{-1}, RR 1.37; 0.9 MET-h · wk^{-1}, RR 1.89 (data adjusted for age, colorectal polyps, endoscopy, parental history, body mass, smoking, use of aspirin, red meat, fibre, folate, and alcohol)
Lee et al. (134)	17,148 M, aged 30–79 yr	L	23-yr follow-up; physical activity reported twice, colon cancer	Relative to energy expenditure >10 MJ · wk^{-1}; >4 MJ · wk^{-1}, RR 1.04; <4 MJ · wk^{-1}, RR 2.00 (data age adjusted)
Lee and Paffenbarger (131)	17,607 M aged 30–79 yr	L	23-yr follow-up, colon cancer	Relative to energy expenditure >10 MJ · wk; if BMI 26 kg · m^{-2} >4 MJ · wk^{-1}, 2.95; if <4 MJ · wk^{-1}, 5.26. All cases >4 MJ · wk^{-1} 0.80; <4 MJ · wk^{-1}, 1.06. (all adjusted for age, BMI, parental history)
Lee et al. (129)	21,807 M, aged 40–84 yr	L	10.9 yr follow-up, colon cancer vs vigorous activity	Relative to none; >5/wk, RR 0.9; 2–4/wk, RR 0.83; 1/wk, RR 0.91 (data adjusted for age, obesity, alcohol)
Severson et al. (206)	7925 M aged 45–64 yr	L	Colon cancer incidence	Relative to hard activity. Moderate activity, RR 0.79; light activity, RR 1.41
Thune and Lund (245)	53,242 M, 28,274 F	L	16-yr follow-up colon cancer incidence	Relative to regular training. Moderately active, RR 0.95 (M), 0.74 (F); sedentary, RR 0.75 (M), 1.19 (F). (all data adjusted for age, BMI, lipids, height, smoking, marital status)
Gerhardsson et al. (78)	163 M, 189 F, 512 matched controls	Cc	Colon cancer; retrospective activity	Relative to very active. Fairly active, RR 1.4, sedentary, RR 1.8 (data adjusted for age, sex, BMI, diet, energy intake, protein, fat, fibre, and browned meat)
Slattery et al. (230)	110 M, 119 F vs 384 controls	Cc	Retrospective intensity and volume of activity colon cancer	Relative to no activity. Hard ("high") intensity, RR 0.27; light ("low") intensity, RR 0.83; relative to light ("low") total activity; high, RR 0.48, moderate, RR 0.50, moderately hard ("high"), RR 0.53 (all data adjusted for age, BMI, gender, smoking, education, income, region of residence)
Slattery et al. (230)	2073 cases, 2466 age- and sex-matched controls	Cc	Retrospective recent and lifetime activity colon cancer	Relative to sedentary; >60 min hard ("vigorous") activity/session, RR 0.68 (time involved per session more important than number of sessions per week) (data adjusted for age at diagnosis, family history, dietary fiber and calcium, aspirin and NSAIDS, cholesterol, energy intake)
Shephard and Futcher (222)	Meta-analysis of colon cancers			22 studies of men, 7 of women; variance-weighted geometric mean relative to sedentary; low-volume, 0.73 (M), 0.74 (M); moderate volume, RR 0.92 (M), 0.83 (F).
Other tumors				
Sesso et al. (205)	1566 F, aged 45.5 yr Free of breast cancer	L	31-yr follow up cancer incidence	Relative to energy expenditure <2.1 MJ · wk^{-1}; 2.1–4.2 MJ · wk^{-1}, RR 0.92; >4.2 MJ · wk^{-1}, RR 0.73 (data adjusted for age and BMI; benefit if postmenopausal only)
Shephard and Futcher (222)	Meta-analysis of breast tumors female reproductive tract tumors prostate tumors			Relative to sedentary; moderate activity, RR 0.71; light activity, RR 0.79. Relative to sedentary; moderate activity, RR 0.96; light activity, RR 0.93 Relative to sedentary; moderate activity, RR 0.94; light activity, RR 0.79

L, longitudinal study; Cc, case control study; RR, relative risk; BMI, body mass index.

FUTURE RESEARCH PRIORITIES

1) More precise methods are needed to assess both relative and absolute energy expenditures in epidemiological surveys.

2) Future studies comparing several relative intensities of effort need to be designed to assure consistent absolute energy expenditures between conditions.

3) There is a need to explore whether there are multiple mechanisms of benefit, with one mechanism being induced by a specified absolute intensity or volume of effort, and another by a specific relative intensity.

4) Given that differing patterns of effort may favor different health outcomes, there is a need to prioritize

TABLE 8. Physical activity and mental health.

Author	Sample	Design	Program	Response
Acute responses				
Tate and Petruzello (242)	20 M aged 22.6 yr	X-over	Control vs 30 min at 55% or 70% $\dot{V}O_{2max}$	Postexercise reduction in anxiety only for 70% $\dot{V}O_{2max}$. Increase of arousal 70% > 55% $\dot{V}O_{2max}$
Berger and Owen (16)	91 university students	X-over	20-min jogging at 55, 75, 79% of max HR	Short-term improvements in all scales of Profile of Mood States, independent of intensity of exercise
Farrell et al. (65)	7 fit M, 27 yr	X-over	80 min at 40 or 60% $\dot{V}O_{2max}$ vs 40 min at 80% $\dot{V}O_{2max}$	Tension reduced only after runs at 60 and 80% $\dot{V}O_{2max}$
Cameron and Hudson (38)	82 M and F, 34 yr Healthy and anxiety states	X-over	Recall of anxiety after five intensities	20% reported intensity-dependent increase of anxiety
Steptoe and Cox (236)	32 F, 18–23 yr	X-over	100 W vs 25 W	Modified POMS shows more tension and anxiety at 100 W more vigor and exhilaration at 25 W
Morgan et al. (158)	120 M	R	Progressive exercise to 150, 160, 170, or 180 beats · min^{-1}	No intergroup differences in depression adjective checklist
Kennedy and Newton (117)	42 M and F aged 39 yr	R	50-min bench-stepping at 60 or 75% max HR	Profile of Mood States shows decrease of tension, depression, fatigue and anger, increase of vigor in both groups. Larger effect on fatigue and anger at harder intensity
Berger and Owen (16)	170 M and F, 22 yr	R	Swimming, body conditioning, yoga and light-intensity exercise vs controls	Yoga and light-intensity work induced largest improvements in POMS mood state
Chronic responses				
Martinsen et al. (147)	99 cases of major depression	Lr	8-wk aerobic vs nonaerobic	No significant difference in response to training
Moses et al. (163)	75 M and F, 18–60 yr	Lr	10 wk of light exercise vs 20 min at 60%, 30 min at 60–75% HRmax vs control	20-min group showed larger improvements in tension and confusion
Sexton et al. (207)	52 symptomatic neurotics	Lr	walking vs jogging, 8 wk	No greater benefit in joggers
Tsutsumi et al. (250)	36 F aged 69 yr	Lr	Moderate or hard ("high") intensity strength training 12 wk, 3/wk vs control	Both training groups showed increased vigor and trend to decreased tension and state anxiety. Moderate intensity also reduced trait anxiety
Brown et al. (34)	69 F, 66 M, aged 55, 51 yr	Lr	Moderate- or light-intensity walking or Tai Chi or walking + relaxation vs control for 16 wk	Moderate exercise reduced tension, depression, anger, confusion and total mood disturbance
Katula et al. (116)	80 older adults	Lr	Light-, moderate-, or hard-intensity exercise	Light exercise decreased anxiety, hard intensity increased anxiety as assessed by State Anxiety Inventory with moderate exercise, increase with high intensity.

Lr, longitudinal, randomized controlled trial; X-over, crossover trial; R, randomized trial; POMS, Profile of Mood States.

outcomes. Specifically, there is a need to assess which outcomes contribute most to quality-adjusted life expectancy.

5) Greater attention should be focused on age-, gender-, and fitness-related differences in physical activity requirements.

6) There is a need to distinguish possible differences in relative and absolute intensity requirements between the prevention and the treatment of disease.

7) Optimal as well as minimal requirements need to be considered, with a view to defining not only thresholds but also ceilings of relative and absolute intensity of effort.

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Chair summary and comments

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The purpose of Howley's paper was to clarify the various terms associated with physical activity and exercise and provide guidelines for consistent interpretation of exercise intensity across various types of exercise. This paper was available to all authors contributing to the symposium and provided a common base of definitions and terminology. Of particular importance in this paper is Table 1, Classification of Physical Activity Intensity, in which intensity descriptors are linked to cut-off points for endurance and resistance exercise. The utilization of these descriptors and cut-offs will be helpful as we attempt to gain a level of standardization in defining exercise intensity.

The LaMonte and Ainsworth paper was focused on methods used to quantify physical activity and energy expenditure and identified potential measurement-related limitations to evaluating the dose-response of physical activity for health outcomes. An important concept that was emphasized in this paper was the distinction between physical activity and energy expenditure and the need to clearly differentiate between them. Physical activity is a behavior that results in energy expenditure. Energy expenditure reflects the volume of physical activity and combines the factors of intensity, frequency, and duration of exercise. This paper also highlighted the many methodological limitations that are present in attempting to measure physical activity in a field setting. Assessing and using energy expenditure in health outcome studies is common because it is believed to provide a better prediction of health outcomes than physical activity. One limitation of using energy expenditure, however, is the inability to break out intensity, frequency, or duration of physical activity required to specifically describe the dose. Even with this limitation, the use of the doubly labeled water method of energy expenditure assessment appears to be the gold standard by which other field measures of energy expenditure and physical activity should be validated (2). These authors also call for the development of an integrated physiological and motion detection system to more objectively measure movement in free-living conditions. This methodology could potentially resolve the long-standing problem associated with accurate field assessment of physical activity.

The third paper in this group by Blair, Cheng, and Holder focused on the question of whether physical activity or physical fitness is more important in defining health outcomes. These authors report that most studies show an inverse dose-response gradient across physical activity categories for most health outcomes, but it is not possible to accurately quantify a general dose-response gradient. They also report that all studies included in their review show an inverse gradient across fitness categories for various health outcomes and that the gradient for fitness is steeper than that for physical activity. When the outcome measure studied is functional limitations (a critical outcome measure for older adults), there is an inverse gradient for both physical activity and fitness with a steeper gradient for fitness. The authors believe that the stronger dose-response gradient for fitness is due to the increased objectivity with which fitness is measured. The misclassification of individuals is significantly higher in studies in which field measures of physical activity are used than for studies using fitness measures. This conclusion supports the contention of LaMonte and Ainsworth that attention must be directed toward the development of more accurate field measures for physical activity. Blair and colleagues also make a clear case for maintaining the public health message on promoting physical activity as opposed to physical fitness.

Roy Shephard addressed the issue of absolute and relative intensity of physical activity in a dose-response context. Shephard made the case for an absolute threshold of approximately 6 METs for over-all health benefits in young adults with a session duration of 30 min and a dose-response gradient beyond this threshold. He also concluded that low or moderate relative intensity of aerobic activity (40–60% $\dot{V}O_{2max}$ or 40–50% $\dot{V}O_2R$) is an appropriate minimal recommendation for population health. This recommendation is particularly important when consideration is given to the advantage of promoting moderate intensity physical activity in a sedentary population. The existence of an absolute threshold for physical activity in order to achieve health benefits is attractive for purposes of public health messaging but would seem to contradict the wide variation of chronic adaptation to exercise that has been demonstrated by Bouchard and colleagues (1,4) and Leon et al. (3).

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Issues of fractionization of exercise (short vs long bouts)

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ABSTRACT

HARDMAN, A. E. Issues of fractionization of exercise (short vs long bouts). *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S421–S427. **Purpose:** To evaluate evidence comparing the influence on health outcomes of different patterns and intensities of exercise with equivalent total energy expenditure. **Methods:** A computerized literature search, with searches of the reference lists of papers identified. **Results:** Studies fell into two categories: 1) comparisons of one continuous session of exercise with several short (≥10-min) sessions of the same total duration; and 2) comparisons of a session of moderate/hard exercise with a session of lower intensity but equivalent energy expenditure. Within each category, studies were found for training effects and for acute effects. Category 1: Several small, randomized controlled trials showed that improvements in measures of cardiorespiratory fitness did not differ significantly between training regimens based on long or short sessions. Acute effects of two short sessions on excess postexercise oxygen consumption were reported to be greater than those of one longer session. By contrast, short-term decreases in postprandial triglyceride concentrations were found to be similar with three short or one long session. Category 2: Higher-intensity training was consistently found to elicit greater increases in $\dot{V}O_{2max}$ than lower-intensity training of longer duration. No conclusion could be drawn for any other outcome. A session of hard/moderate exercise may be more likely than to induce short-term negative energy balance than light exercise. Findings on the comparability of sessions of different intensities on blood lipids and glucose/insulin dynamics are conflicting. **Conclusion:** Further research is required before the principle of fractionization can be endorsed with confidence. **Key Words:** ACCUMULATION, SPLIT SESSIONS, INTENSITY, DURATION, LONG, SHORT

Epidemiological studies have found an inverse relationship between the total energy expended in leisure time physical activity and health outcomes. These include a lower risk of all-cause mortality (16), cardiovascular morbidity and mortality (16,27), Type II diabetes (18), hypertension (29), and site-specific cancers (36,37). Some activities contributing to high totals of energy expenditure seem likely to have been performed at least partly on an intermittent basis, for example, walking (24), climbing stairs (27,28), gardening (24), and repair work (16). Survey evidence therefore suggests that several short sessions of moderate physical activity during the day influence health outcomes in a positive manner, at least when they contribute to a high total energy expenditure. Two approaches have been adopted in testing this proposition experimentally: first, comparing continuous exercise with several short sessions and, second, "trading" intensity for duration.

The purpose of this review is to evaluate the evidence available to address the following questions: 1) Are several short sessions of exercise as effective in influencing health outcomes as one longer session of the same total duration? 2) When the energy expended is equivalent, are the effects of low intensity exercise on health outcomes similar to those of higher intensity exercise? The relevant literature is concerned with exercise—as opposed to physical activity—because of the need to be confident that energy expenditure is comparable between different regimens. For each question, evidence has been considered separately for training effects elicited over weeks or months and for acute, short-term effects lasting hours or days.

A literature search was made through PubMed from 1980 to August 2000, using combinations of the following terms: accumulation, exercise, training, intermittent, continuous, short bout(s)/session(s), long bout(s)/sessions, splitting distance/time. A large number of items were found using the terms intermittent and continuous, but, with one exception, these compared the effects on fitness measures of training regimens based on long, continuous sessions with those based on "interval training", i.e., repeated high-intensity efforts separated by brief recovery periods within one session. This literature was disregarded because a key feature of the concept of accumulation of activity in the present context is that bouts of activity are engaged in on two or more occasions during the day. The reference lists of the papers selected were checked for further publications. Review is limited to full papers and to those comparing different patterns/intensities of exercise within a single study. Measures of cardiorespiratory fitness are assumed to be health outcomes because of the evidence for lower cardiovascular

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and all-cause mortality in men and women with higher levels of fitness (3).

ONE LONG SESSION OF EXERCISE VERSUS SEVERAL SHORT EXERCISE SESSIONS PER DAY

Long-Term Training Effects

Only three randomized controlled trials were found, with a total of 156 subjects (Table 1). Of these, one examined the influence of running training in male students (11) and two the influence of brisk walking in middle-aged sedentary people (25,40). Brisk walking (20,21) and jogging (9) were the interventions in three randomized uncontrolled trials and brisk walking in one controlled nonrandom trial (39) (Table 1). Measures of fitness—with one exception (39), including maximal oxygen uptake ($\dot{V}O_{2max}$)—were the only outcome measures common to all papers. The majority of these trials found no difference in improvements in $\dot{V}O_{2max}$ between groups performing long or short exercise sessions. Decreases with training in heart rate or blood lactate concentration during standard submaximal exercise also showed similar improvements in cardiorespiratory fitness with long or short sessions (25,39,40). Only one study (9) found a statistically greater increase in $\dot{V}O_{2max}$ with long sessions of running than with short. Exceptionally, one study (40) reported no increase in $\dot{V}O_{2max}$ with brisk walking. This finding was probably due to low statistical power, however.

Besides $\dot{V}O_{2max}$, the only outcome measure reported across a number of studies is body mass. Three studies found similar decreases after short- or long-bout regimens (9,20,21), and one found a greater decrease after short-bout sessions (25). Two studies reported data on plasma lipids: relative to controls, one found no changes (11) and one found a decrease in low density lipoprotein (LDL) cholesterol (40) in long-bout (35 min) and intermediate-bout (15 min) walkers but not in short-bout (10 min) walkers.

Evidence statement. Limited evidence from small, randomized, controlled trials shows that improvements in cardiorespiratory fitness from exercise regimens comprising several short sessions per day are as effective as those comprising longer continuous sessions. Findings from uncontrolled or nonrandomized trials are inconsistent (Evidence Category B). No comparable body of evidence exists for other health outcomes, including changes in body mass.

Short-Term, Acute Effects

A single session of exercise elicits quantitative and qualitative changes to energy metabolism, some of which probably mediate effects on health outcomes (17). These acute effects may be important in the longer term if exercise is undertaken regularly and frequently. Table 2 summarizes the findings from laboratory studies of the effect of fractionizating exercise on excess postexercise oxygen consumption (EPOC) (2 studies) and postprandial plasma triglyceride (TG) concentrations (2 studies). Both studies of EPOC found that this was significantly greater after two short sessions than after one longer session of equivalent duration (1,22). The effect of exercise pattern was strong—EPOC was 40% and 115% greater after short sessions—but small in relation to daily energy turnover. One postprandial study reported the effects of prior prolonged exercise (13) and the other the effects of 30 min of exercise during a day-long observation period (26). Their findings were consistent in that each pattern of exercise (3 short sessions vs 1 long) elicited similar decreases to plasma TGs. The studies included in Table 2 were all small ($N \geq 6 \leq 18$), and only one employed exercise applicable to sedentary middle-aged people (30 min of brisk walking) in a relevant subject group (26). The remaining studies involved hard exercise and/or longer exercise sessions and/or young, physically active subjects.

Evidence statement. Four counterbalanced laboratory studies with two different health outcome measures show that two short sessions of moderate/hard exercise are at least as effective as a single session of the same total duration (Evidence Category B).

TRADING INTENSITY FOR DURATION: LONGER, LOWER INTENSITY SESSIONS VERSUS SHORTER SESSIONS OF HIGHER INTENSITY

This model is relevant indirectly to issues of fractionization because it enshrines the principle that the total energy expended in exercise mainly determines its influence on health outcomes. Studies of both different training regimens and single exercise sessions have employed this design, in which gross exercise energy expenditure is held constant. A limitation is the existence of qualitative differences between exercise sessions, for example, in substrate utilization, cardiovascular responses, and hormonal milieu. There is some difficulty, too, because—although gross energy expenditure during exercise may be the same—the net energy expenditure of the higher intensity exercise will be somewhat greater. The importance of this factor depends on the intensities of exercise being compared (increasing with the difference in intensity between comparison trials) and the duration of the session(s). One further caveat relevant to studies of walking may be added; because the energy cost of walking increases nonlinearly at fast speeds, controlling for walking distance may not control for energy expenditure. Both these effects increase the likelihood that hard exercise will be found to have a greater influence than light exercise on health outcomes related to energy expenditure.

Long-Term Training Effects

Four longitudinal studies have compared training regimens of different intensities but equivalent energy expenditure (Table 3). Outcomes included measures of cardiorespiratory fitness, body mass and fatness, and blood lipids. Two randomized, controlled trials were found, using walking (10) and walking/jogging (15) as the mode of exercise, as well as two randomized uncontrolled studies using cy-

TABLE 1. Studies comparing the training effects of different exercise patterns: single long versus two or more short [a] sessions per day.

Reference	Design	Population	Duration	Interventions	Results	Comments
Ebisu, 1985 (11)	Randomized, controlled	Untrained male students ($N = 53$)	10 wk	1, 2 or 3 sessions; running 3 (increasing to 6) miles·d^{-1}, 3 d·wk^{-1} at ~73% $\dot{V}O_{2max}$	Increases in $\dot{V}O_{2max}$[b] and decreases in run time similar with all three patterns	No changes in blood lipids, relative to controls
DeBusk et al., 1990 (9)	Randomized	Middle-aged men ($N = 36$)	8 wk	1 or 3 sessions; jogging for 30 min·d^{-1}, 5 d·wk^{-1} at ~62% $\dot{V}O_{2max}$	Increase in $\dot{V}O_{2max}$ (7.6%) with short sessions less than with long (13.9%); decreases in body mass similar	Long group spent more time above specified HR range
Jakicic et al., 1995 (20)	Randomized	Sedentary, overweight, middle-aged women ($N = 56$)	20 wk	1 or multiple 10-min sessions; 'Primarily' walking for 20 (increasing to 40) min·d^{-1}, 5 d·wk^{-1} at ~65% $\dot{V}O_{2max}$	Increases in $\dot{V}O_2$peak (long 13.7%, short 16.3%), decreases in body mass (long 7.2%, short 9.7%) and BP similar with both patterns	Low-energy, low-fat diet. Short group did 19% more exercise in 15-min sessions
Murphy and Hardman, 1998 (25)	Randomized, controlled	Middle-aged women ($N = 47$)	10 wk	1 or 3 sessions; brisk walking for 30 min·d^{-1}, 5 d·wk^{-1} at ~66% $\dot{V}O_{2max}$	Similar increases in $\dot{V}O_{2max}$ (long 8.5%, short 8.3%); decrease in body mass greater with short walks	Subjects undertook not to change diet
Woolf-May et al., 1998 (39)	Controlled	Low-active people aged, 40–71 yr ($N = 28$ men, $N = 21$ women)	18 wk	Long (20–40 min) or short (10–15 min) sessions; brisk walking for 60 (increasing to 200) min·wk^{-1} at ~66% $\dot{V}O_{2max}$	Similar decreases in HR during submaximal stepping; no changes to blood lipids	Changes to $\dot{V}O_{2max}$ not reported
Woolf-May et al., 1999 (40)	Randomized controlled	Sedentary, age, 40–77 yr ($N = 19$ men; $N = 37$ women)	18 wk	Long (20–40 min), intermediate (10–15 min); or short (5–10 min) sessions; brisk walking for 60 (increasing to 200) min·wk^{-1} at ~67% $\dot{V}O_{2max}$;	No changes in $\dot{V}O_{2max}$; decreases in blood lactate during submaximal exercise similar for long and short; changes to apolipoprotein ratios and decreases to LDL cholesterol with long and intermediate	Underpowered—NS increases in $\dot{V}O_{2max}$ were 13% (long), 16% (intermediate), and 13% (short) vs—4% for control
Jakicic et al., 1999 (21)	Randomized	Overweight women mean, age 37 yr ($N = 73$)	72 wk	1 or multiple 10-min sessions; exercise 'similar to brisk walking' for 20 (increasing to 40) min·d^{-1}, 5 d·wk^{-1}	Increases in $\dot{V}O_{2max}$ (long 23%, short 13%), decreases in body mass (long 6.5%, short 4.1%), and changes in body composition not significantly different between patterns	At 24 months, increase in $\dot{V}O_{2max}$ greater for long session group

[a] $\dot{V}O_{2max}$ in mL·kg^{-1}·min^{-1}. If not reported, estimated from group means for absolute values or from data on % max HRR. If $\dot{V}O_{2max}$ not reported, % $\dot{V}O_{2max}$ estimated from other indices of exercise intensity

TABLE 2. Studies comparing acute effects of different exercise patterns; single long vs two or more short sessions per day.

Study[a]	Population	Comparison	Results	Comments
Kaminsky et al., 1990 (22)	Women aged 30 yr ($N = 6$)	50 min running vs two 25-min sessions at 70% $\dot{V}O_{2peak}$	Total EPOC[b] greater after short sessions (58 kJ) than after long (27 kJ)	EPOC small with both patterns
Almuzaini et al., 1998 (1)	Men aged 23 y ($N = 10$)	30 min cycling vs two 15-min sessions at 70% $\dot{V}O_{2max}$	Total EPOC greater after short sessions (155 kJ) than long (111 kJ)	EPOC small with both patterns
Gill et al., 1998 (13)	Men, mean age 30 yr ($N = 18$, 3 mildly hyperlipidemic)	90 min running vs three 30-min sessions at 60% $\dot{V}O_{2max}$ vs no exercise	Similar (18%) decrease in postprandial TGs after long or short sessions; only short reduced insulin response	Low power to detect differences in insulin response ($N = 6$)
Murphy et al., 2000 (26)	Middle-aged people ($N = 3$ men, $N = 7$ women)	30 min brisk walking at 60% $\dot{V}O_{2max}$ vs three 10-min sessions vs no exercise	Decrease in postprandial TG 12% with both patterns of walking	9 subjects normolipidemic, 1 hyperlipidemic

[a] Repeated measures, counterbalanced (not stated in ref. 22) and randomized (not stated in ref. 13).
[b] EPOC, excess postexercise oxygen consumption expressed in energy units.

TABLE 3. Longitudinal studies comparing training effects of different regimens where duration of exercise was manipulated to expend the same energy at two different intensities.

Reference	Design	Population	Duration	Interventions	Results	Comments
Gaesser and Rich, 1984 (12)	Randomized	Men aged 20–30 yr ($N = 16$)	18 wk	Cycling 3 d·wk^{-1}; 45% $\dot{V}O_{2max}$ for 50 min vs 80–85% $\dot{V}O_{2max}$ for 25 min expending ~1257 kJ/session, increasing to 1467 kJ	Similar increases in $\dot{V}O_{2max}$ (17 and 20%) and decreases in body fat (1.3–1.4 kg) with moderate and hard; no changes in lipids	Subjects 'encouraged to continue with normal dietary habits'
Gossard et al., 1986 (15)	Randomized, controlled	Sedentary men, mean age 49 yr ($N = 64$)	12 wk	Walking/jogging 5 d·wk^{-1}; 42–60% VO_{2max} for ~52 min vs 63–81% $\dot{V}O_{2max}$ for ~37 min, expending ~1467 kJ/session	$\dot{V}O_{2max}$ increased with moderate (8%) but more with hard (17%)	Home-based; intensity estimated from ambulatory HR (based on $\dot{V}O_2$/HR relation)
Duncan et al., 1991 (10)	Randomized, controlled	Sedentary women aged 20–40 yr ($N = 59$)	24 wk	Walking 5 d·wk^{-1}; 4.8 km·d^{-1} at 4.8 km·h^{-1} vs 6.4 km·h^{-1} vs 8.0 km·h^{-1}; 4.8 kph ≈ 56% max HR (light); 6.4 kph ≈ 67% max HR (moderate); 8.0 kph ≈ 86% max HR (hard)	$\dot{V}O_{2max}$ increased in all groups, but more in 8.0 km·h^{-1} group (16%) than in 4.8 km·h^{-1} (4%); decrease in body fat in 4.8 km·h^{-1} group; no changes in lipids, relative to controls	42% drop-out rate; controls showed 6% decrease in $\dot{V}O_{2max}$ and 4% increase in body fat; diets monitored—no changes
Branch et al., 1999 & 2000 (4, 5)	Randomized	Sedentary women, mean age 33 yr ($N = 18$)	12 wk	Cycling 3–4 d·wk^{-1}; 40% $\dot{V}O_{2max}$ vs 80% $\dot{V}O_{2max}$, expending 628 kJ (increasing to 1560 kJ)/session	Increases in $\dot{V}O_{2max}$ 14% with light, 21% with hard: similar decreases in submaximal HR and R values; no changes in body mass or fatness	Baseline $\dot{V}O_{2max}$ value 29.5 mL·kg^{-1} min^{-1}

cling (4,5,12). Both of the randomly controlled trials report statistically significant increases in $\dot{V}O_{2max}$, relative to controls, in the groups training at lower intensity but found that these increases were not as great as those observed in the group(s) training at higher intensity (10,15). By contrast, neither of the uncontrolled trials (4,5,12) found a significant difference in the increase in $\dot{V}O_{2max}$ between groups. Effects on body mass and fatness, where these were found, were inconsistent. Only Duncan and colleagues (10) reported changes to lipids (increase in high-density lipoprotein cholesterol), but these were not significantly different from those observed in controls. The issue of potentially confounding effects of diet on changes to body mass and/or composition or blood lipids received little attention, with only one study (10) reporting monitoring data.

Evidence statement. Two randomly controlled trials show that training at a low/moderate intensity for 45–50 min per session 3–5 d per week increases $\dot{V}O_{2max}$ in sedentary persons but that higher-intensity exercise of equivalent energy expenditure leads to greater increases (Evidence Category B).

Short-Term, Acute Effects

Seven of 13 studies were concerned with outcomes related to energy balance and these are presented in Table 4a. The findings of six studies comparing effects on blood lipids or glucose/insulin dynamics are summarized in Table 4b.

Only two of the studies of factors influencing energy balance included a no-exercise control trial (19,35). Both investigated postexercise energy intake and reported no increase in short-term intake with either light exercise (35% $\dot{V}O_{2max}$) or hard exercise (68% or 75% $\dot{V}O_{2max}$). In line with this finding, Klausen et al. (23) found no difference in total energy intake the day following light or moderate exercise. Only one study (19) considered the net energy expenditure of exercise, reporting that relative energy intake (total energy intake minus energy expenditure of exercise above the resting level) was significantly lower after hard exercise than after light exercise. Three of four (uncontrolled) studies found that EPOC was higher after moderate (7) or hard exercise (31,33) than after light exercise, and one (32) found no difference. This contrasts with evidence on split exercise sessions referred to above and suggests that exercise intensity *per se* may influence the magnitude of EPOC.

One controlled (38) and three uncontrolled (8,14,23) studies report data on plasma lipids and related variables. Decreases in fasting TGs and in postprandial lipemia after light and hard exercise sessions expending 4.2 MJ were strikingly similar (38). By contrast, other reports showed either no effect of prior exercise on fasting TGs (8) or that TGs were lower the morning after moderate exercise than after light exercise (23). Two studies, both with control (no exercise) trials, compared effects of exercise intensity on measures of glucose/insulin dynamics, but their findings are inconsistent. One found that the insulin response during an oral glucose tolerance test was lower than control after hard but not after light exercise (2). The other, in Type II diabetics, found very similar decreases in postprandial insulin concentration and increases in glucose disposal after moderate and hard exercise (6).

Evidence statement. Based on literature reviewed here, there is some evidence that moderate/hard exercise may be more likely to induce negative energy balance than light exercise expending an equivalent amount of energy. Findings on the comparability of exercise sessions of different intensity in influencing plasma lipids or glucose/insulin dynamics are conflicting (Evidence Category C).

Future Research Priorities

Two priorities are clear: first, there is a need for more robust data for the small number of outcomes reviewed here; and second, additional outcome measures need to be examined. It is essential that the health outcomes being compared must, *a priori,* be those for which a consistent body of evidence already exists. If an effect on the specified out-

TABLE 4a. Studies comparing the acute effects of two exercise sessions of different intensities but similar total gross energy expenditure[a]; outcome measures related to energy balance.

Study	Population	Comparison	Results	Comments
Thompson et al., 1988 (35)	Men aged 19–29 yr ($N = 15$)	Cycling at 35% $\dot{V}O_{2max}$ vs 68% $\dot{V}O_{2max}$, expending 17.2 kJ/kg^{-1} body mass (~1304 kJ) vs no exercise	Hunger suppressed more by 68% but effect short-lived (≤20 min); no effect of either exercise pattern on postexercise (1 h) energy intake	Exercise did not increase subsequent food energy intake
Broeder et al., 1991 (7)	Men aged 25–30 yr ($N = 5$)	Walking at 30% $\dot{V}O_{2max}$ vs 60% $\dot{V}O_{2max}$, expending 3.02 MJ.	EPOC[2] and attenuation of postfeeding increase in RER greater after 60% $\dot{V}O_{2max}$than after 30% $\dot{V}O_{2max}$	Suggests harder exercise has greater effects on energy balance; low power
Sedlock et al., 1989 (33)	Male triathletes, mean age 26 yr ($N = 10$)	Cycling at 50% $\dot{V}O_{2max}$ vs 75% $\dot{V}O_{2max}$, expending 1.26 MJ	EPOC greater in magnitude and duration after 75% (122 kJ and 33 min) than after 50% (59 kJ and 20 min)	EPOC 5% of gross exercise energy expenditure after moderate and 10% after hard
Sedlock, 1991 (32)	Women aged 26 yr ($N = 7$)	Cycling at 40% $\dot{V}O_{2max}$ vs 60% $\dot{V}O_{2max}$, expending 850 kJ	No significant differences in EPOC	EPOC 53% longer (NS) after moderate, i.e. opposite direction to earlier study by this author
Imbeault et al., 1997 (19)	Men aged 18–40 yr ($N = 11$)	Walking/running at 35% $\dot{V}O_{2max}$ vs 75% $\dot{V}O_{2max}$, expending 2050 kJ vs no exercise	No differences in total energy intake (single buffet meal); intake relative to net exercise energy expenditure 16% less after 75% $\dot{V}O_{2max}$ than after 35%	Well-controlled study. Subjects had high $\dot{V}O_{2max}$ (56.7 mL·kg^{-1} min^{-1})
Phelain et al., 1997 (31)	Women aged 22–31 yr ($N = 8$)	Cycling at 50% $\dot{V}O_{2max}$ vs 75% $\dot{V}O_{2max}$, expending 2095 kJ	EPOC greater after 75% (172 kJ) than after 50% (92 kJ); fat oxidation lower ($P = 0.07$) after 75%	EPOC incompletely measured; $\dot{V}O_2$ still elevated 3 h after hard exercise
Klausen et al., 1999 (23)	Young (28–35 yr) and old (68–73 yr) (men ($N = 16$) and women ($N = 16$))	Cycling at 30% $\dot{V}O_{2max}$ for 60 min vs 60% $\dot{V}O_{2max}$ for 30 min	% energy intake from fat day after exercise higher after 60% $\dot{V}O_{2max}$ but no difference in total energy intake	Neither age nor gender influenced these effects

[a] Exercise energy expenditure values are gross figures; net expenditure therefore slightly greater for the higher-intensity session.
[b] EPOC, excess postexercise oxygen consumption expressed in energy units.

come of an established/reference exercise pattern (say, for Question 1 continuous bouts of ≥ 30–40 min or, for Question 2, hard exercise) cannot be detected, no comparison with the effects of split sessions or with a longer session of light exercise may be made. Adequate statistical power is also an obvious prerequisite. Thus, studies need to focus on established health outcomes, employ exercise models likely to elicit large effects and avoid making more comparisons than subject numbers permit. Study of a challenging exercise regimen (high intensity and/or long duration) may be justified in order to obtain a clear answer to a specific question, with subsequent replication in a larger group of sedentary individuals with more moderate exercise when "proof of concept" is established.

The "minimum" recommendation for 30 minutes of physical activity on most days (30) can be achieved by numerous combinations of short bouts of different duration, reflecting the continuum from a structured exercise program to a physically active lifestyle. Comparison of sessions of less than 10 minutes may be ill advised. One reason is that interventions, especially long-term, based on shorter sessions than this are difficult to implement (in practice, people

TABLE 4b. Studies comparing the acute effects of two exercise sessions of different intensities but similar total gross energy expenditure; outcome measures related to lipoprotein lipids and glucose/insulin dynamics.

Study	Population	Comparison	Results	Comments
Davis et al., 1992 (8)	Men runners aged 28 yr ($N = 10$)	Running at 50% $\dot{V}O_{2max}$ for 90 min vs 75% $\dot{V}O_{2max}$ for 60 min	No significant changes in blood lipids measured 1, 24, 48, or 72 h after exercise	Subjects had low TGs and cholesterol, high HDL cholesterol
Gordon et al., 1994 (14)	Men runners aged 25 yr ($N = 12$)	Running at 60% $\dot{V}O_{2max}$ vs 75% $\dot{V}O_{2max}$, to expend 3352 kJ	Only hard exercise increased HDL cholesterol; plasma LPL increased but no significant difference between these increases (moderate 13%; hard 27%)	Increase in HDL cholesterol ∝ 1/baseline concentration; data corrected for plasma volume changes
Tsetsonis and Hardman, 1996 (38)	Physically active aged 28 ($N = 5$ men; $N = 4$ women)	Walking at 30% $\dot{V}O_{2max}$ for 180 min vs 60% $\dot{V}O_{2max}$ for 90 min vs no exercise	Postprandial TGs reduced and fat oxidation increased to similar degree by light and moderate sessions; only moderate intensity reduced postprandial insulin	Considerable reductions to lipemia (~30%)
Klausen et al., 1999 (23)	Young (28–35 yr) and old (68–73 yr) (men ($N = 16$) and women ($N = 16$))	Cycling at 30% $\dot{V}O_{2max}$ for 60 min vs 60% $\dot{V}O_{2max}$ for 30 min.	Morning after exercise, fasting TGs lower after moderate than after light exercise (0.91 vs 0.98 mmol·L^{-1})	No influence of age or gender
Ben-Ezra et al., 1995 (2)	Untrained women, mean age 23 yr ($N = 24$)	Walking at 40% $\dot{V}O_{2max}$ for 87 min vs 70% $\dot{V}O_{2max}$ for 50 min vs no exercise	Insulin response to oral glucose tolerance test significantly lower than control (by 15%) after hard exercise; no effect of light exercise	Nonresponders; 6 women showed no reduction in insulin after hard exercise, 9 no reduction after light
Braun et al., 1995 (6)	Overweight women mean age 44 with type II diabetes ($N = 8$)	Walking at 50% $\dot{V}O_{2max}$ vs 75% $\dot{V}O_{2max}$ vs no exercise; two walks·d^{-1} during 2 d before testing, expending 523 kJ/session	Decreases in insulin response to test meal and increases in rate of glucose disposal similar after moderate and hard sessions	Glucose disposal corrected for differences in plasma insulin concentration

tend to exercise in bouts longer than specified (20,40)) and standardize. A personal view is that the research base underpinning physical activity recommendations will be better served by robust studies of 10- to 15-minute bouts, which will complement intervention studies of lifestyle activities already underway.

SUMMARY AND CONCLUSIONS

Only a small number of studies were found that addressed the question that was directly relevant to issues of fractionization (Question 1). These are characterized by rather small numbers, and, in practice, all involved sessions of 10 minutes or more. Many studies were underpowered for the number of exercise interventions compared and so are at risk of Type-II error. By far, the commonest classification of exercise intensity adopted was $\%\dot{V}O_{2max}$, and this may not be the most appropriate approach for sedentary persons with low $\dot{V}O_{2max}$ values (34) who are the main target population for physical activity recommendations. The range of health outcomes examined was small, namely, indices of cardiorespiratory fitness, body mass and composition, EPOC, postexercise energy intake, plasma lipids, and aspects of glucose/insulin dynamics. Further research is required before the principle of fractionization can be endorsed with confidence. This may not have equal validity for different health outcomes.

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Dose response between total volume of physical activity and health and fitness

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ABSTRACT

OJA, P. Dose response between total volume of physical activity and health and fitness. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S428–S437. **Purpose:** Studies published in 1990s were evaluated for the possible dose response between the total volume of physical activity and the fitness and health outcomes, and for the characteristics of the dose response relations. **Methods:** Nineteen observational studies and 15 randomized trials were identified. The scope of the studies was on primary prevention among inactive, healthy, middle-aged and elderly men and women. MET-min·wk^{-1} was used as the primary volume measure. No studies addressing specifically the volume-outcome dose response were identified. **Results:** The cross-sectional and follow-up studies suggested a graded dose response of the volume of physical activity with all-cause mortality, stroke and several coronary heart disease risk factors. The benefits were apparent among both men and women. Nonrandomized and uncontrolled randomized trials exhibited no clear dose response relationship, whereas the randomized controlled trials showed a crude graded dose response between the exercise volume as measured by MET-min·wk^{-1} and $\dot{V}O_{2max}$ but not between volume and disease risk factors. An apparently clearer dose response was seen between the intensity of physical activity and the $\dot{V}O_{2max}$ response. These data do not allow for quantitative characterization of the observed dose response relations between physical activity volume and health and fitness. **Conclusion:** Fairly strong evidence indicates a crude dose response between the total volume of weekly physical activity and cardiorespiratory fitness but only weak evidence for a dose response of activity volume and health measurers. **Key Words:** MET-MINUTES, RANDOMIZED CONTROLLED TRIALS, MIDDLE-AGED MEN, WOMEN

Several recent reviews (18,29,41,42,48,50) have emphasized the importance of the total amount of physical activity rather than its specific characteristics, such as intensity, frequency, and bout duration for health benefits. This has been observed with regard to mortality (12,41), morbidity (2,55), and several disease risk factors (4,6,10,17,23,26,52).

Although most of the review authors suggest a dose response between the total volume of physical activity and the health outcomes and some a minimum or desirable threshold (12,17,26,42,47,55), the evidence comes mostly from observational studies. Consequently, the precise quantitative characteristics of the dose response remain undefined. Furthermore, there is little evidence based on studies specifically designed for the analysis of the volume-outcome dose response.

Therefore, the purpose of this review was to examine: 1) whether there is a dose response between total volume of physical activity and indexes of health and fitness, and if so for which outcome measures. 2) What are the characteristics of the identified dose-response relations?

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METHODS

For this review studies of four types were searched: 1) observational cross-sectional and case-control studies, 2) epidemiological follow-up studies, 3) non- or incompletely randomized experimental studies, and 4) randomized controlled experimental trials. The general inclusion criteria were: 1) studies focused on primary prevention; 2) subjects were middle-aged and elderly relatively inactive and nonsymptomatic men and women; 3) there was a quantitative description of the volume of physical activity; and 4) the outcome measures in the observational studies were to include indexes of mortality, morbidity, or cardiovascular or metabolic risk factors, and in the experimental studies cardiorespiratory performance, body weight, and cardiovascular or metabolic risk factors.

An additional inclusion criteria for the experimental studies was a quantitative specification of the intervention duration and the frequency, bout duration, and intensity of the employed exercise program. The intensity had to be described as walking pace or percent maximal effort. Walking pace was converted to METs according to Ainsworth et al. (1). Percent HR_{max} was first converted to % $\dot{V}O_{2max}$ by the formula % HR_{max} = 0.7305 (%$\dot{V}O_{2max}$) + 29.95 (22). Percent $\dot{V}O_{2max}$ was first transformed to $\dot{V}O$ based on the reported baseline $\dot{V}O_{2max}$, which was then divided by 3.5 to yield the intensity as multiples of resting metabolic rate (MET). Further inclusion criteria for the experimental studies were a direct measure of $\dot{V}O_{2max}$.

The literature search included the following databases from 1995 on for the observational studies and from 1990 on

TABLE 1. Cross-sectional and case-control studies on the relation between the volume of physical activity and heart disease risk factors.

Study	Subjects	Design	Physical Activity	Outcome Variables	Results
Kokkinos et al. (25)	Men = 2906 (30–64 yr)	Cross-sectional	Weekly running distance (RD), miles·wk^{-1}	Serum lipids: trigylceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C)	Decreasing trend of TC, TG and LDL-C, and increasing progressive trend of HDL-C with increasing RD
Mayer-Davis et al. (35)	Men = 660, women = 807 (40–69 yr), normal to mild NIDDM	Cross-sectional	Estimated total energy expenditure (EEE), kJ·d^{-1} (kcal·d^{-1})	Insulin sensitivity (IS)	Stepwise increase in IS by quintiles of EEE
Mensink et al. (36)	Men = 5943, women = 6039 (25–69 yr)	Cross-sectional	Weekly LTPA at low, moderate, and high intensity, kcal·wk^{-1}	CHD risk factors: total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), blood pressure (BP) and BMI	Significant linear regression coefficients of HDL-C at low and high LTPA, TG at high LTPA, DBP at high LTPA and BMI at high LTPA among men, and HDL-C at moderate LTPA, TG at low and high LTPA, SBP at high LTPA, DBP at low LTPA and BMI at all levels of LTPA among women
Sacco et al. (44)	Women = 600, men = 467 (70±12.4 yr)	Case-control	Duration of weekly LTPA, hr/week	Ischemic stroke (IS)	Odds ratio of IS by LTPA: no vs. <2 hr/wk: 0.42 no vs. 2–<5 hr/wk: 0.35 no vs. ≥5 hr/wk: 0.31
Siscovick et al. (49)	Men = 1022, women = 1252 (≥65 yr)	Cross-sectional	Weekly LTPA at moderate intensity, kcal·wk^{-1}	CHD risk factors: blood pressure, glucose metabolism, blood lipids, coagulation factors	Significant decreasing trend of triglycerides and increasing trend of HDL-cholesterol in men, and decreasing trend of diastolic blood pressure, 2-hour glucose, fasting and 2-hour insulin, total cholesterol and LDL-cholesterol in women by tertiles of LTPA
Wareham et al. (53)	Men = 73, women = 89 (30–49 yr)	Cross-sectional	Physical activity level (PAL) total energy expenditure devided by BMR per day	Metabolic cardiovascular syndrome (MCS)	Odds ratios of MCS by PAL: 1. quartile: 1.0 2. quartile: 0.49 (0.14–1.60) 3. quartile: 0.25 (0.05–0.94) 4. quartile: 0.33 (0.08–1.18)
Williams (56)	Men = 7059 competitive runners (45.7±9.5 yr)	Cross-sectional	Running distance (RD), km·wk^{-1}	Heart disease risk factors: abdominal fatness (AF), blood pressure (BP), HDL cholesterol, LDL cholesterol, triglycerides (TG)	Significant decrease of AF and TG and increase of HDL-C in men, and decrease of AF and increase of HDL-C in women with increasing RD

for the experimental studies: MEDLINE, Sport, Ebsco Academic Search Elite, Cochrane Systematic Reviews, and Dare.

Observational Studies

Cross-sectional and case-control studies. Six cross-sectional studies were identified (Table 1). Two of them (35,53) utilized a measure of total activity that covered all or most daily activities: the former was based on continuous heart-rate monitoring and calculation of energy expenditure thereof, and the latter a comprehensive recall of all daily activities. Wareham et al.'s study (53) with young adult men and women yielded decreasing odds ratios (OR) of metabolic cardiovascular syndrome by increasing quartiles of total physical activity. However, only the OR for the third quartile with respect to the lowest one was statistically significant (OR 0.25 with confidence interval of 0.05–0.94). Other ORs had wide confidence intervals, thus yielding nonsignificant relations.

Mayer-Davis et al.'s (35) study assessed insulin sensitivity in quintiles of total daily energy expenditure among middle-aged men and women with normal to mild non-insulin–dependent diabetes mellitus. They found a progressive step-wise increase in insulin sensitivity by the quintiles of energy expenditure ranging from about 1.2 to 2.0 $min^{-1}\cdot\mu U^{-1}\cdot mL^{-1}\cdot 10^{-4}$ from the lowest to the highest quintile.

Two cross-sectional studies measured leisure-time physical activity (LTPA). Siscovick et al. (49) determined moderate-intensity LTPA among elderly men and women and related that to 17 coronary heart disease (CHD) risk variables. Among men, significant trends of risk factors by tertiles of physical activity were found for high-density lipoprotein (HDL)-cholesterol (increasing) and triglycerides (decreasing), and among women for diastolic blood pressure, three measures of glucose metabolism and total- and low-density lipoprotein (LDL)-cholesterol (all decreasing). In the study by Mensink et al. (36), weekly total LTPA was assessed separately for low-, moderate-, and high-intensity activities, and they were related to CHD risk factors by regression analysis. In men, significant beneficial relations, as indicated by linear regression coefficients, were found for most risk factors at high-intensity LTPA but for fewer at moderate- and low-intensity LTPA. Among women, BMI showed inverse significant relation to LTPA at all intensity levels, but fewer relations were found for other risk factors and at the lower-intensity levels.

Two cross-sectional studies examined the relation between the volume of physical activity and disease risk factors among regular middle-aged runners using weekly running distance as the measure of exercise volume. Kokkinos et al. (25) found a systematic step-wise increase in HDL cholesterol and decrease in triglycerides with increasing running distance in men. Williams (56) demonstrated a

TABLE 2. Prospective follow-up studies on the relation between the volume of physical activity and mortality and disease risk factors.

Study	Subjects	Design	Physical Activity	Outcome Variables	Results
Fried et al. (11)	Women = 2962, men = 2239 (≥65 yr)	5-yr prospective follow-up	Energy expenditure of moderate to vigorous LTPA, kcal·wk^{-1}	All-cause mortality (ACM)	Relative risk of ACM by LTPA: <67.5 vs 67.5–472.5: 0.78 (0.60–1.00) vs 472.5–980.0: 0.81(0.63–1.05) vs 980.0–1890.0: 0.72(055–0.93) vs >1890: 0.56(0.43–0.74)
Haapanen et al. (13)	Men = 1072 (35–63 yr)	10-yr prospective follow-up	Weekly net energy expenditure (WEE) of leisure-time, household and commuting physical activity	All-cause ((ACM) and CVD mortality (CVDM)	Relative risk of ACM by WEE: >2.100 kcal·wk^{-1} 1:1.00 1.500–2.100 kcal·wk^{-1} 1:1.74(0.87–3.50) 800–1.500 kcal·wk^{-1} 1:1.10(0.55–2.21) <800 kcal·wk^{-1} 1:2.74(1.46–5.14) Relative risk of CVDM by WEE: >2.100 kcal·wk^{-1} 1:1.00 1.500–2.100 kcal·wk^{-1} 1:1.59(0.56–4.49) 800–1.500 kcal·wk^{-1} 1:0.99(0.34–2.87) <kcal·wk^{-1} 1:3.58(1.45–8.85)
Haapanen et al. (14)	Men = 1340, women = 1500 (35–63 yr)	10-yr prospective follow-up	Weekly net energy expenditure (WEE) of leisure-time, household and commuting physical activity	Nonfatal CHD, hypertension (HT), diabetes (D)	Relative risk of CHD by Wee: Men: high 1.00, moderate 1.33(0.78–2.27), low 1.98(1.22–3.23) Women: high 1.00, moderate 0.73(0.38–1.39), low 1.25(0.72–2.15) Relative risk of HT by WEE: Men: high 1.00, moderate 1.66(1.07–2.57), low 1.73(1.13–2.65) Women: high 1.00, moderate 0.94(0.59–1.50), Low 1.16(0.75–1.79) Relative risk of D by WEE: Men: high 1.00, moderate 1.21(0.63–2.31), low 1.54(0.83–2.84) Women: high 1.00, moderate 1.17(0.50–2.70), low 2.64(1.28–5.44)
Hakim et al. (15)	Men = 707 (61–81 yr)	12-yr prospective follow-up	Walking distance (WD), miles·d^{-1}	All-cause (ACM) and CHD mortality (CHDM)	Relative risk of ACM by WD: 0–0.9 vs 2.1–8.0: 1.9(1.3–2.9) 0–0.9 vs 1.0–2.0: 1.6(1.2–2.2) 1.0–2.0 vs 21–8.0: 1.2(0.8–1.7) Nonsignificant for CHDM
Hakim et al. (16)	Men = 2678 (71–93 yr)	2 to 4 yr prospective follow-up	Walking distance (WD), miles·d^{-1}	CHD mortality (CHDM)	Relative risk of CHDM by WD: <0.25 vs >1.5: 2.2(1.3–3.7) 0.25–1.5 vs >1.5: 1.8(1.1–3.0) <0.25 vs 0.25–1.5: 1.2(0.8–1.8)
Hayashi et al. (19)	Men = 6017 (35–60 yr) normotensive	9-yr prospective follow-up	Duration of walk to work (WW), min	Incidence of hypertension (HT), SBP ≥ 160 and/or DBP ≥ 95 mm Hg	Relative risk of HT by WW: 0–10: 1.00 11–20: 0.91(0.77–1.08) >20: 0.70(0.59–0.95) WW as cont.: 0.88(0.78–0.98)
Lee et al. (28)	Men = 17321 (46 yr)	26- or 22-yr prospective follow-up	Weekly energy expenditure of LTPA, kJ·wk^{-1}	All-cause mortality (ACM)	Relative risk of ACM by LTPA: 1. quintile: 1.00 2. quintile: 0.94(0.86–1.04) 3. quintile: 0.95(0.86–1.05) 4. quintile: 0.91(0.83–1.01) 5. quintile: 0.91(0.82–1.00)
Lee and Pattenberger (30)	Men = 11130 (58±8.95 yr)	11-yr prospective follow-up	Energy expenditure of LTPA, (kcal·wk^{-1}), walking distance (WD), km·wk^{-1}	Incidence of stroke (S)	Relative risk of S by LTPA: <1000 vs 1000–1999: 0.76(0.59–0.98) vs 2000–2999: 0.54(0.38–0.76) vs 3000–3999: 0.78(0.53–1.15) vs ≥4000: 0.82(0.58–1.14) Relative risk of S by WD: <5 vs ≥20: 0.71(0.52–0.96)
Lissner et al. (32)	Women = 1267 (38–60 yr)	20-yr prospective follow-up	Global classification of LTPA and occupational pa (OPA) during three life periods	All-cause mortality (ACM)	Relative risk of ACM by OPA past 12 mo: medium vs low: 0.28(0.17–0.46) high vs low: 0.24(0.14–0.43) Relative risk of ACM by LTPA past 12 mo: medium vs low: 0.56(0.39–0.82) high vs low: 0.45(0.24–0.86) Significant RRs also for earlier life periods
Manson et al. (34)	Women = 72488 (40–65 yr)	8-yr prospective follow-up	Weekly physical activity (WPA) MET-H·wk^{-1}	Incidence of coronary events (CE)	Relative risk of CE by quintiles of WPA: 1. quintile: 1.00 2. quintile: 0.77(0.62–0.96) 3. quintile: 0.65(0.52–0.82) 4. quintile: 0.54(0.42–0.69) 5. quintile: 0.46(0.36–0.60)
Sesso et al. (46)	Women = 1564 (37–69 yr)	31-yr prospective follow-up	Weekly physical activity (WPA), kcal·wk^{-1} (includes stairs climbed, blocks walked, and sport played)	Incidence of CVD	Relative risk of CVD by blocks walked: <4·d^{-1}: 1.00 4–9·d^{-1}: 0.89(0.63–1.25) >9·d^{-1}:0.73(0.51–1.06) Nonsignificant for total WPA, stairs climbed and sports played.

TABLE 2. *Continued*

Study	Subjects	Design	Physical Activity	Outcome Variables	Results
Thune et al. (51)	Men = 2681, women = 3626 (20–49 yr)	7-yr prospective follow-up, (sustained activity study)	Global LTPA classification combining intensity and frequency: sedentary, moderate, hard, very hard	Serum lipids: triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and BMI	Significant decreasing progressive trend of TG, TC, HDL-C and BMI, and increasing trend of HDL-C in both men and women (except of HDL-C)
Weller and Corey (54)	Women = 6620 (50.3±15.0 yr)	7-yr prospective follow-up	Daily energy expenditure (DEE) $kcal \cdot kg^{-1} \cdot d^{-1}$	All-cause mortality (ACM), CVD mortality, fatal MI	Odd ratio of ACM by quartile of DEE: 1. quartile: 1.00 2. quartile: 0.86(0.66–1.13) 3. quartile: 0.68(0.51–0.91) 4. quartile: 0.73(0.54–1.00) By quartile of non-leisure DEE: 1. quartile: 1.00 2. quartile: 0.66(0.56–0.87) 3. quartile: 0.68(0.51–0.89) 4. quartile: 0.71(0.50–0.87)

decrease in abdominal fatness and an increase in HDL cholesterol with increasing weekly running distance in both men and women.

Sacco et al. (44) utilized a case-control design in studying the relation of LTPA with ischemic stroke among elderly men and women. The odds ratio of stroke decreased substantially (ORs ranging from 0.42 to 0.31) with increasing LTPA.

These observational studies show consistently an inverse association between physical activity and cardiovascular disease (CVD) risk factors and stroke among middle-aged and elderly men and women. The results suggest a graded dose response of the volume of physical activity with several CVD risk factors and stroke incidence.

Epidemiological Follow-up Studies

The follow-up studies fall into three broad categories with respect to the type of physical activity that was assessed: total physical activity, leisure-time physical activity (LTPA), and walking (Table 2).

Weller and Corey (54) assessed the total daily energy expenditure (kcal per kilogram of body weight per day) for leisure activities, nonleisure activities, and the total activity as their sum based on recall. According to their results, inclusion of the household nonleisure activities in the assessment is important, because they represent 82% of the total activity of the women in the study. Odds ratios of all-cause mortality varied from 0.86 to 0.68 for the second to fourth quartiles of total daily activity and from 0.66 to 0.71 for the nonleisure daily activity, the latter all being statistically significant. There was no distinct dose response with increasing activity and the mortality risk.

In two Finnish studies (13,14), weekly total physical activity, including leisure-time sports, exercise and physical recreation, leisure-time and household chores, and physically active commuting to and from work, was assessed. The lowest quartile (<800 $kcal \cdot wk^{-1}$) was found to have significant 2.74-fold relative risk of all-cause and 3.58-fold risk of cardiovascular mortality, relative to the highest quartile (>2.100 $kcal \cdot wk^{-1}$) (13). With the same activity assessment, they (14) found in men a significant risk of nonfatal CHD incidence for the lowest activity (RR = 1.98), and of hypertension for both the lowest (RR = 1.73) and for the middle third (RR = 1.66), and an increasing but nonsignificant risk of diabetes. In women, the lowest third of activity showed increased but nonsignificant risk of CHD and hypertension, and a significant 2.64-fold risk of diabetes, relative to the highest third. In these two studies a dose-response trend is observable, but a significant increase in the mortality and morbidity risk is more obvious in the lowest activity class only.

Most of the epidemiological studies have quantified leisure-time physical activity. Weekly LTPA was shown to decrease the risk of coronary events (34) in a graded fashion, all-cause mortality in partially graded fashion (11), and stroke in a U-shape fashion (30), whereas no reduced risk was found in all-cause mortality by Lee et al. (28) and in CVD incidence by Sesso et al. (46).

Global classification of LTPA with both frequency and intensity taken into account decreased the risk of all-cause mortality in a graded way in the study by Lissner et al. (32). Thune et al. (51) showed graded decreasing trends in serum lipids with similar LTPA classification.

In the studies with quantified amounts of walking as the activity measure, Hakim et al. found reduced risk of all-cause mortality (15) and reduced risk of CHD mortality (16) with increasing amount of walking, both in a graded fashion. Only a relatively large volume of walking was found to be protective against CVD incidence by Sesso et al. (46) and against hypertension by Hayashi et al. (19).

Nine of the reviewed epidemiological studies included women as subjects. The results are quite consistent in showing that the health benefits of physical activity are present also in women and that the benefits are similar to those of men.

These epidemiological studies give further support to the earlier conclusions stating that the health benefits of physical activity are strongly linked to the total amount of activity and that the health benefits accrue in approximate proportion to the total amount of activity performed (42). Although the earlier evidence consisted primarily of CHD mortality as the health outcome and was limited almost exclusively to middle-aged men, a new element in the recent evidence expands the health benefits to all-cause mortality, stroke, and CHD risk factors and, importantly, shows substantial health benefits to women equal to those of men.

However, the recent evidence is not very powerful in exploring the relative importance of total volume of physical activity versus the mode, intensity, and bout duration of activity. This is mainly due to the crudeness of the assessment tools applicable in epidemiological studies. Furthermore, the existing epidemiological studies are flawed by the narrow consideration of physical activity as primarily leisure-time exercise. Only three (13,14,54) of the reviewed studies measured the nonleisure physical activity in depth and demonstrated that the nonleisure activities account by far for the majority of daily physical activity. Thus, an important future challenge in epidemiological research is to consider properly all domains of physical activity, namely work and study, transport, daily chores, and leisure.

Experimental Studies

Randomized without control group and nonrandomized studies. Four randomized studies with no control group (3,5,8,24) and one nonrandomized study (40) with specific enough description of the exercise dose for total volume assessment were identified (Table 3). The subjects in all studies were previously inactive, healthy, middle-aged men and/or women. The studies compared different exercise intensities (3), intermittent versus continuous (5), and structured versus lifestyle (9,24) protocols. One study (40) had only one intervention, but it was included, because the activity mode, golf, necessitates an unusually long bout duration and thus leads to large total volume. Because none of the studies focused in particular on the total volume of exercise, the range of weekly exercise dose is rather narrow (from 526 to 887 MET-hours), with the exception of the golf study, and consequently the data are not very strong for the examination of the effects of the total volume of exercise.

Most of these studies showed a significant but modest, up to 10%, increase in $\dot{V}O_{2max}$ (Table 4). Exceptionally large increases were seen in both low- and high-intensity groups of women in the study by Branch et al. (3). Four studies reported changes in body weight, but only one (40) showed a statistically significant decrease. Decreased systolic blood pressure was reported in two studies (5,9) and no change in one study (40). Blood lipids were reported in three studies. Significant increases were seen in HDL cholesterol (9,24,40), but other lipid changes were small and/or nonsignificant.

No apparent dose response of exercise volume and outcomes is seen in these results. By far, the largest weekly dose was in the golf study (40). The observed changes were rather consistent but not particularly large, except that of submaximal metabolic performance (blood lactate at standard submaximal work), which was not measured in other studies.

Randomized Controlled Studies

Eleven randomized controlled trials were included in the review (Table 5). Subjects in these studies were 20- to 65-yr-old men and/or women, healthy and previously inactive, with the exception of one study (43), in which the women were somewhat older. The programs varied considerably in duration, from 10 wk to 18 months. The studies included one to three intervention groups in addition to the control group. All studies reported actual program duration, weekly exercise frequency, and bout duration, thus providing basis for the total volume calculation. Exercise intensity was reported as controlled walking pace (7) or as physiological intensity relative to maximum (all other studies), allowing for study specific estimate of the exercise intensity in METs. Again, none of the studies evaluated specifically the effects of different total volume of exercise. However, the volume range between single treatment groups turned out to be considerable, from 257 to 1571 MET-min·wk^{-1}.

All but one (31) study showed statistically significant increase in $\dot{V}O_{2max}$, ranging from a few percent to over 20% (Table 6). Body weight changes were reported in eight studies. They amounted to a few percent in either direction and were mostly nonsignificant. Small and nonsignificant reductions or no change in systolic blood pressure was reported in four studies. Similarly, small and mostly nonsignificant changes of blood lipids were reported in seven studies. Consistent lipid changes were seen only in one study (27) employing fast walking as the exercise mode: 3% decrease in total cholesterol, 4% increase in HDL cholesterol, 8% increase in total cholesterol to HDL-cholesterol ratio, and 18% reduction in triglycerides. Two stud-

TABLE 3. Summary table of experimental studies with randomized without control group or non-randomized design on the dose-response between exercise volume and fitness and health.

Study	Subjects	Program Duration (wk)	Exercise Groups	Frequency (times·wk^{-1})	Bout Duration (min)	Intensity		Exercise Volume (MET min)	
						Reported	Estimated MET[a]	Session (d)	Week
Branch et al. (3)	Women = 18 (20–40 yr)	12	1. low intensity	3.3	62	40 % $\dot{V}O_{2max}$	3.4	211	696
			2. high intensity	3.4	39	80 % $\dot{V}O_{2max}$	6.7	261	887
Coleman et al. (5)	Women = 27, men = 5 (18–55 yr)	16	1. intermittent	3–6(p)[c]	2232[b]	68 % HR_{max}	5.4	167	753
			2. continuous	3–6(p)	1923	68 % HR_{max}	5.3	142	637
			3. choice	3–6(p)	2100	68 % HR_{max}	5.1	149	669
Dunn et al. (9)	Men = 116, women = 119 (35–60 yr)	26	1. structured	5(p)	20–60(p)	50—85 % $\dot{V}O_{2max}$			
			2. lifestyle	7(p)	30(p)	moderate			
King et al. (24)	Men = 149, women = 120 (50–65 yr)	104	1. high int. group	2.7	40(p)	73–88 % HR_{max}	5.2	208	562
			2. high int. home	2.7	40(p)	73–88 % HR_{max}	5.3	212	572
			3. low int. home	4.5	30(p)	60–73 % HR_{max}	3.9	117	526
Parkkari et al. (40)	Men = 55 + 55 (48–64 yr)	30	1. golf	2.5	240	59 % HR_{max}	4.7	1080	2700

[a] see the text; [b] total in 16 weeks; [c] prescribed.

TABLE 4. Effects of randomized with no control or nonrandomized physical activity interventions on cardiorespiratory fitness and CVD risk factors.

Study/Exercise Group	$\dot{V}O_{2max}$ (mL)		Weight (kg)		SBP (mm Hg)		Tchol (mmol)		HDL-C (mmol·L^{-1})		Tchol/HDL-C		Triglyc (mmol·L^{-1})		Other	
	Pre	%Δ Sig.[a]	Pre	%Δ Sig.	Pre	%Δ Sig.	Pre	%Δ Sig.	Pre	%Δ Sig.	Pre	%Δ Sig.	Pre	%Δ Sig.	Pre	%ΔS
Branch et al. (3)																
Low intensity	NR[b]	17 +	65.7	3 −												
High intensity	NR[b]	21 +	60.2	0 −												
Coleman et al. (5)																
Intermittent	32.8	6	(70.7)	−0.5	110.5	−2										
Continuous	34.5	8 +	(67.1)	−0.9 −	113.8	−5 +										
Choice	34.8	6	(72.4)	−0.5	117.6	−7										
Dunn et al. (9)																
Structured	26.5	5 +	82.6	−1 −	126.3	3 +	5.6	−2 +	1.3	−4 +	4.9	4 +	1.9	4 −		
Lifestyle	26.8	3 +	83.0	0 −	124.0	−3 +	5.5	−2 (+)	1.3	−2 −	4.7	1 −	1.8	−6 −		
King et al. (24)																
High int. group	26.8	4 +							1.4	3 −						
High int. home	27.5	9 +							1.3	4 +						
Low int. home	27.1	6 +							1.3	8.5 +						
Parkkari et al. (40)															La at 7 MET	
Golf	36.1	−1 ⊕	83.0	−2 ⊕	128.0	0 −	5.9	−3 −	1.3	4 ⊕	4.5	5 ⊕	1.7	−8 −	1.85	−15⊕

[a] Statistical significance:
⊕ Statistically significant between group difference of change at $P < 0.05$.
\+ Statistically significant within group change at $P < 0.05$.
− Statistically nonsignificant within group change.
[b] NR not reported.

ies (37,39) reported consistent improvement in submaximal metabolic performance.

Because of the small and mostly inconsistent changes in the risk factors, these randomized controlled trials provide sufficient data for the analysis of the dose response of the total volume of exercise and the outcome only with regard to $\dot{V}O_{2max}$. Figure 1 summarizes the percent changes of $\dot{V}O_{2max}$ as the function of exercise volume in MET-minutes per session. The $\dot{V}O_{2max}$ changes vary from −2 to +22% with volume range from 100 to 400 MET-minutes with no distinct dose response. When the dose is expressed in MET-min·wk^{-1} (Fig. 2), there appears to be a crude dose response, particularly among within study observation points, but for a given dose the variance in the response remains large. When exercise intensity is considered independent of the volume, the scatter (Fig. 3) shows clearer dose response, particularly if the studies by Santiago et al. (45) and Leon et al. (31) are considered as outliers. However, even then the response variance at the lower intensity range is considerable.

None of the reviewed nonrandomized and randomized exercise trials have been designed to analyze specifically the dose response of the total exercise volume and health and fitness outcomes. A further weakness in the available evidence is that the reported responses in health outcomes are inconsistent and small, at best, for any meaningful analysis. Nevertheless, comparative estimates of the intervention vol-

TABLE 5. Summary table of randomized controlled trials on the dose response between exercise volume and fitness and health.

Study	Subjects	Program Duration (wk)	Exercise Groups	Frequency (times·wk^{-1})	Bout Duration (min)	Intensity		Exercise Volume (MET min)	
						Reported	Estimated MET[a]	Session (d)	Week
Duncan et al. (7)	Women = 102 (20–40 yr)	7 + 17	1. Strollers	4.5	60	3.4–4.8 km·h^{-1}	2.5, 3.3	150, 198	675, 891
			2. Brisk walkers	4.5	45	4.5–6.4 km·h^{-1}	3.5, 4.7	157, 211	709, 952
			3. Aerobic walkers	4.5	36	5.6–8.0 km·h^{-1}	4.0, 6.7	144, 270	648, 1215
Heinonen et al. (20)	Women = 105 (52–53 yr)	77	1. Endurance	3.2	30	72 % $\dot{V}O_{2max}$	5.5	165	528
			2. Callisthenics	2.6	30	43 % $\dot{V}O_{2max}$	3.3	99	257
Hendriksen et al. (21)	Men = 87, women = 35 (25–65 yr)	24	1. Cycling men	3.3	58	68 % HR_{max}	6.2	348	1148
			2. Cycling women	3.0	43	75 % HR_{max}	4.5	236	709
Kukkonen-Harjula et al. (27)	Men = 55, women = 62 (30–55 yr)	15	1. Walking	3.8	42	65–75 % $\dot{V}O_{2max}$	8.0	336	1277
Leon et al. (31)	Men = 20 (22–44 yr)	12	1. treadmill Walking + stair climbing	5	45 + 7	55,82 % HR_{max}	3.5, 7.2	207	1035
Loimaala et al. (33)	Men = 83 (35–55 yr)	20	1. walk-jog	4.4	34.5	55 % HR_{max}	3.7	128	562
			2. jog	4.1	32	75 % HR_{max}	6.6	211	866
Murphy and Hardman (37)	Women = 47 (31–57 yr)	10	1. contin. walk	4.5	30	75 % HR_{max}	5.0	150	675
			2. interm. walk	4.5	3 × 10	73 % HR_{max}	4.7	141	634
Oja et al. (38)	Men = 93 (40 yr)	10	1. running	2.9	40.3	79.5 % $\dot{V}O_{2max}$	8.3	334	970
			2. skiing	2.9	42.0	78.0 % $\dot{V}O_{2max}$	7.8	328	950
Oja et al. (39)	Men = 38, women = 30 (20–65 yr)	10	1. walking	3.9	67.5	52 % $\dot{V}O_{2max}$	5.3	358	1395
			2. cycling	3.9	62.0	63.5 % $\dot{V}O_{2max}$	6.5	403	1571
Ready et al. (43)	Women = 79 (61.3±5.8 yr)	24	1. walking	2.9	59	60 % $\dot{V}O_{2max}$	4.0	236	684
			2. walking	4.9	57	60 % $\dot{V}O_{2max}$	3.8	217	1061
Santiago et al. (45)	Women = 27 (22–44 yr)	40	1. walk uphill	3.6	53(est.)	72 % HR_{max}	5.2	276	994

TABLE 6. Effects of randomized physical activity interventions on cardiorespiratory fitness and CVD risk factors.

Study/Exercise Group	$\dot{V}O_{2max}$(mL)		Weight, kg		SBP, mmHg		Tchol, mmol		HDL-C, mmol/L		Tchol/HDL-C		Triglyc, mmol/L		Other	
	Pre	%Δ Sig.[a]	Pre	%Δ Sig.	Pre	%Δ Sig.	Pre	%Δ Sig.	Pre	%Δ Sig.	Pre	%Δ Sig.	Pre	%Δ Sig.	Pre	%Δ Sig.
Duncan et al. (7)															%fat	
Strollers	31.8	4 ⊕	62.0	1 −	108	−3 −	4.82	−2 −	1.34	6 +	3.79	−7 +	1.10	−8 −	27.9	−6 ⊕
Brisk walkers	32.4	9 ⊕	64.2	0 −	109	1 −	4.93	−4 −	1.53	4 −	3.37	−7 −	0.92	0 −	26.2	−5 □
Aerobic walkers	30.6	16 ⊕	60.3	2 −	105	0 −	4.62	5 −	1.39	6 +	3.52	−2 −	0.94	12 −	27.5	−4 □
Heinonen et al. (20)																
Endurance	26.9	12 ⊕	71.0													
Callisthenics	27.1	10 □	68.0													
Hendriksen et al. (21)																
Men 0–6 mo	40.5	6 +	82.8													
Women 0–6 mo	31.2	−2 −	70.7													
Men 6–12 mo	39.6	7 +	82.8													
Women 6–12 mo	28.9	9 +	70.7													
Kukkonen-Harjula et al. (27)															Fibrinogen	
Walking	40.2	14 ⊕	80.8[b]	−1 ⊕			5.24	−3 ⊕	1.20	4 □	0.26	8 ⊕	1.14	−18 ⊕	3.16	0 □
			66.8[c]	−2 ⊕												
Leon et al. (31)																
Treadmill walking	35.6	0−	83.0	0 −	119	0 −	185	0 −	37	8 −			1.13	−16 +		
Loimaala et al (33)																
Walk-jog	38.4	11 □	88.9													
Jog	37.3	15 ⊕	89.2													
Murphy and Hardman (37)															$\dot{V}O_2$ at La. 2.0	
Continuous	28.1	9 ⊕	66.7	−1 □	124	−4 □									19.3	18 ⊕
Intermittent	27.8	8 ⊕	66.5	−3 ⊕	125	−6 □									18.9	14 ⊕
Oja et al. (38)																
Running	36.4	13 +	79.2	2−			5.89	NR −	1.48	NR −						
Skiing	35.0	17 +					5.95	NR −	1.45	NR −						
Oja et al. (39)															La at 85 % max	
Walking	35.7	2 −					5.04	2 −	1.43	6 +	0.29	7 +	1.03	4 −	3.90	−3 −
Cycling	35.8	7 +													5.21	−21 +
Men			80.5	NR −												
Women			65.4	NR −												
Ready et al. (43)																
3 times/wk	23.2	12 ⊕	71.1	−1 ⊕	134	−5 □	5.9	−5 □	1.52	14 □			1.3	−8 □		
5 times/wk	27.8	8 ⊕	68.1	0 □	131	−4 □	6.0	0 □	1.56	10 □			1.3	8 □		
Santiago et al. (45)																
Walk uphill	31.5	22 +	64.4	−2 −			4.70	−2 −	1.68	−2 −			0.74	−4 −		

[a] Statistical significance:
+ statistically significant within group change at $P < 0.05$.
− statistically nonsignificant within group change.
⊕ statistically significant between group difference of change at $P < 0.05$.
□ statistically nonsignificant between group difference of change at $P < 0.05$.
NR, not reported.
[b] Men, [c] Women.

umes allow for indirect exploration of the dose response for $\dot{V}O_{2max}$. Nonstatistical evaluation of the data yields no or only a weak dose response when the volume is expressed as MET-minutes per session and somewhat clearer dose response with MET-min·wk^{-1} as the volume measure. Further examination of the exercise intensity alone suggests that it appears to be more important dose characteristic than exercise volume.

Future Research Priorities

1) No studies designed specifically to examine the dose response of the total volume of physical activity and fitness and health outcomes were identified. As the issue of how much physical activity is needed for desired benefits is of great relevance from both individual and public health perspective, there is an urgent need for such studies, both observational and experimental. In these studies, other key elements of the physical activity dose, i.e., frequency, intensity, bout duration, and intervention duration, should be controlled for.

2) Because only few consistent responses in the health outcomes were reported in the experimental studies, most having healthy men and women as subjects, it is suggested that higher-risk subjects were recruited for more substantial response. Some studies suggest that a metabolic response to standard submaximal exercise may be more sensitive to change than traditional risk factors.

3) Most of the observational studies have focused primarily on leisure-time physical activity. As two studies suggest, leisure-time activity accounts for a minor proportion of the total activity. Therefore, in future studies, it is important to register all activity types, i.e., work and study, transportation, and domestic chores, in addition to leisure-time activity.

4) As the volume of physical activity has been assessed by a variety of measures in the earlier studies, comparison across studies is difficult. It is suggested that MET is used as the standard measure of the intensity of physical activity and MET-min·wk^{-1} as the measure of total volume for better comparison.

CONCLUSIONS

This systematic review of 19 observational studies and 15 randomized trials among middle-aged, inactive, healthy

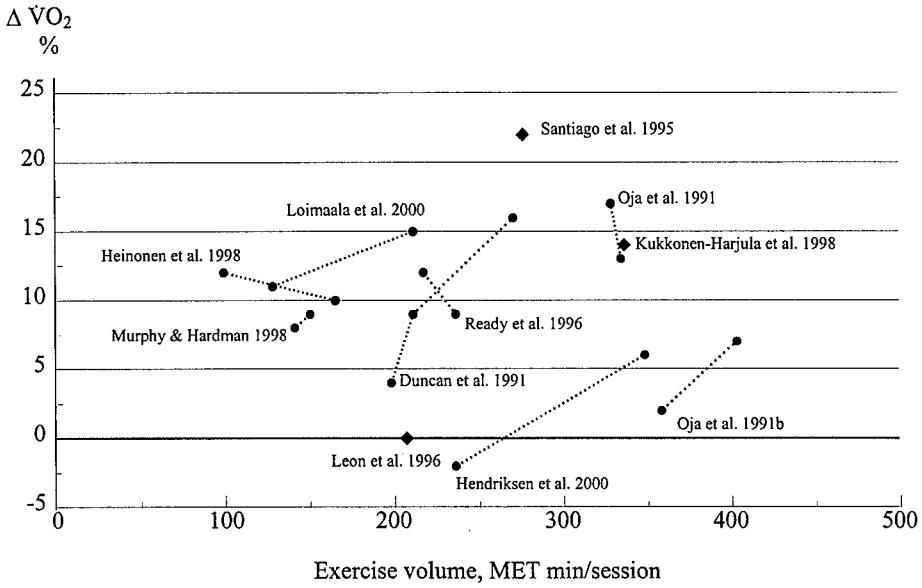


FIGURE 1—Percent change of $\dot{V}O_{2max}$ as a function of total exercise volume (MET minutes per session) in randomized controlled trials. References as in the text.

men and women was aimed to substantiate and clarify the earlier suggestive evidence on the dose response between total volume of physical activity and the health and fitness outcomes. Among the identified and selected studies, no one addressed specifically this question. These limited data warrant the following conclusions:

1) Cross-sectional and follow-up observational studies suggest a graded positive dose response between the total volume of physical activity and all-cause mortality, stroke, and several CHD risk factors among both men and women.

2) Nonrandomized and uncontrolled randomized trials indicate no clear dose response between the volume and either the fitness or the health outcomes.

3) Randomized controlled trials show a crude graded dose response between the total weekly volume and cardiorespiratory fitness as measured by $\dot{V}O_{2max}$. The analysis suggested that the intensity of physical activity may be a stronger dose characteristic than the total volume for fitness response. Quantitative characterization of the dose-response relation between the exercise volume and $\dot{V}O_{2max}$ is limited by the large variance of the response at a given volume.

4) No clear volume-health outcome dose response was identified in the experimental studies, due to a small or nonexistent response.

In summary, there is fairly strong evidence (Category B) to show a graded dose response between the total volume of weekly physical activity and cardiorespiratory fitness but only weak evidence (Category C), based on observational studies and mostly unsubstantiated by experimental studies, for a dose response of activity volume and health measures.

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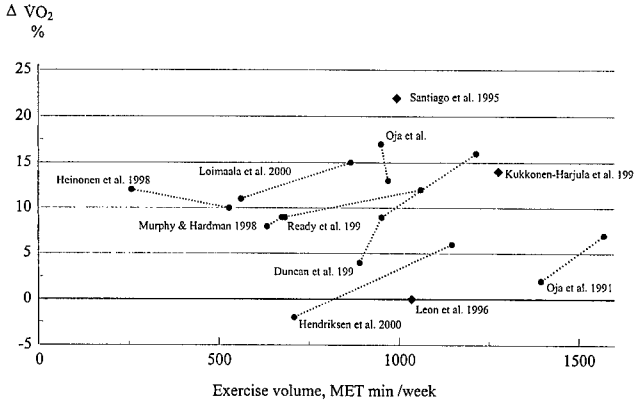


FIGURE 2—Percent change of $\dot{V}O_{2max}$ as a function of total exercise volume (MET min·wk^{-1}) in randomized controlled trials. References as in text.

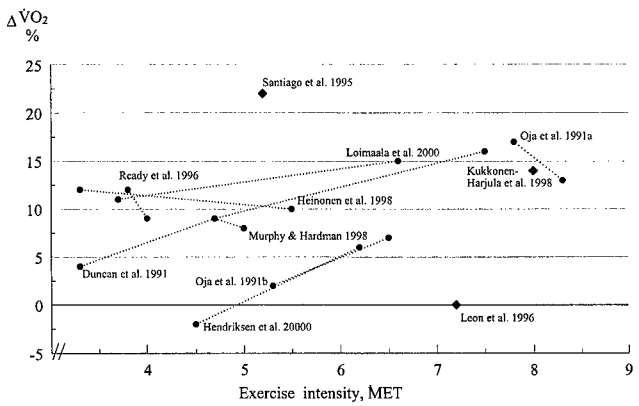


FIGURE 3—Percent change of $\dot{V}O_{2max}$ as a function of exercise intensity (MET) in randomized controlled trials. References as in the text.

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The acute versus the chronic response to exercise

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ABSTRACT

THOMPSON, P. D., S. F. CROUSE, B. GOODPASTER, D. KELLEY, N. MOYNA, and L. PESCATELLO. The acute versus the chronic response to exercise. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S438–S445. **Purpose:** There is strong and consistent evidence that a single exercise session can acutely reduce triglycerides and increase high-density lipoprotein (HDL) cholesterol (HDL-C), reduce blood pressure, and improve insulin sensitivity and glucose homeostasis. Such observations suggest that at least some of the effects on atherosclerotic cardiovascular disease (ASCVD) risk factors attributed to exercise training may be the result of recent exercise. **Results:** These acute and chronic exercise effects cannot be considered in isolation. Exercise training increases the capacity for exercise, thereby permitting more vigorous and/or more prolonged individual exercise sessions and a more significant acute effect. The intensity, duration, and energy expenditure required to produce these acute exercise effects are not clearly defined. The acute effect of exercise on triglycerides and HDL-C appears to increase with overall energy expenditure possibly because the effect maybe mediated by reductions in intramuscular triglycerides. Prolonged exercise appears necessary for an acute effect of exercise on low-density lipoprotein (LDL) cholesterol (LDL-C) levels. The acute effect of exercise on blood pressure is a low threshold phenomenon and has been observed after energy expenditures requiring only 40% maximal capacity. The acute effect of exercise on glucose metabolism appears to require exercise near 70% maximal, but this issue has not been carefully examined. **Conclusions:** Exercise has definite acute effects on blood lipids, blood pressure, and glucose homeostasis. Exercise also has acute effects on other factors related to atherosclerosis such as immunological function, vascular reactivity, and hemostasis. Considerable additional research is required to define the threshold of exercise required to produce these putatively beneficial effects.

Isolated exercise sessions elicit acute, transient cardiovascular, and metabolic responses. Frequent repetition of these isolated sessions produces more permanent adaptations, referred to as the exercise training response. Many of the potentially favorable changes in atherosclerotic cardiovascular disease (ASCVD) risk factors previously considered to require long-term exercise training are now known to have both an acute and chronic exercise component. These risk factors include blood lipids, blood pressure, and serum glucose, but many of the nonstructural changes that occur with exercise training are also affected by recent exertion. This overview will discuss the acute exercise effect and its influence on selected ASCVD risk factors.

INTERACTION OF THE ACUTE AND CHRONIC EXERCISE EFFECTS

The acute exercise response and the chronic adaptations to exercise training cannot be viewed in isolation. Haskell (26) has proposed four patterns for an acute exercise effect (Fig. 1).

a) Exercise may acutely reduce a risk factor, the effect dissipates rapidly and has no influence on the response to subsequent exertion.

b) The acute exercise effect may accrue in a cumulative yet diminishing manner so that subsequent sessions result in asymptotically smaller benefit.

c) Exercise training increases exercise capacity, which permits larger individual exercise sessions and a greater acute effect.

d) Low-level exercise may produce small reductions in risk that are not readily detectable in clinical studies but have benefit when applied to a large enough population.

These patterns are not exclusive, and each may contribute to the acute exercise response, depending on the subject and the risk factor. Indeed, many of the acute exercise changes in risk factors have been reported after prodigious amounts of exercise. Untrained individuals may be incapable of the exertion required to affect a risk factor emphasizing the interdependence of fitness and exercise training on the acute exercise response.

On the other hand, the absence or inconsistency of significant acute exercise effects in reports in untrained subjects doing moderate amounts of exercise does not mean that changes would not be detectable with sufficiently reliable measurement techniques and sufficient sample sizes. Many of the studies mentioned below used

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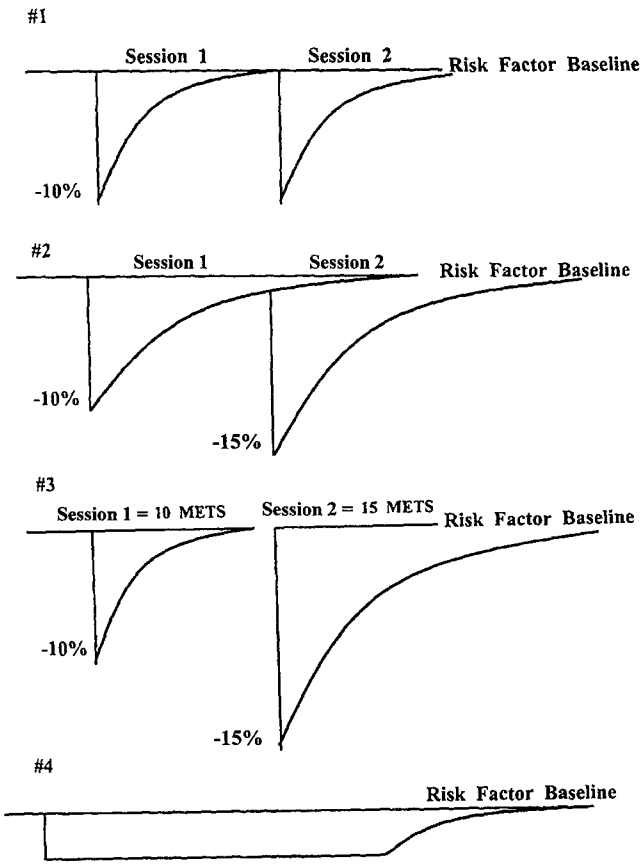


FIGURE 1—Potential patterns for the acute effect of exercise on cardiovascular risk factors. See text for details; adapted from ref. 26.

prolonged endurance exercise to determine whether any acute changes occurred. Subsequent studies have attempted to define the threshold of exercise required but used sample sizes of 10–20 people. The absence of changes in small study populations does not imply that such changes would not be detectable in larger samples. This review will attempt to identify the dose of exercise required for an acute exercise effect when available, but most studies reported below are really proof of concept reports. The minimal amount of exercise required to produce an important, acute exercise effect cannot be defined with certainty from the available literature.

QUALITY OF THE EVIDENCE

The conclusions presented in this review are generally based on Category A Evidence. The amount of information supporting an acute exercise effect on ASCVD risk factors is extensive and generally consistent. That said, it must also be appreciated that published reports probably overestimate an acute exercise effect because of the tendency for positive results to be submitted and accepted for publication. This is especially true in this field of research where the finding of an effect from a singular exercise session would be unexpected to many reviewers and therefore deemed worthy of publication.

THE ACUTE EXERCISE EFFECT ON LIPIDS AND LIPOPROTEINS

Endurance athletes have serum high-density lipoprotein (HDL) cholesterol (HDL-C) concentrations 10 to 20 $mg \cdot dL^{-1}$ or 40–50% higher than their sedentary counterparts (52,62,64,71). Triglyceride (TG) levels are 20% lower. Low-density lipoprotein (LDL) cholesterol (LDL-C) concentrations are often approximately 5–10% lower (52,62,64). The major HDL apoproteins (Apo) AI and AII are often 25% and 15% higher (62,64) whereas Apo B is generally 6–7% lower (64). Oral fat tolerance and the ability to clear intravenously administered triglycerides may be enhanced by 50% (52). The activity of enzymes involved with lipid metabolism is also altered with increases in lipoprotein lipase activity (LPLA) of approximately 13% and decreases in hepatic triglyceride lipase activity (HTGLA) as great as 27% (64). At least some of these differences are due to an acute effect of recent exercise. There are over 100 articles and abstracts that have examined the acute effect of exercise on lipids, as shown in Table 1. The results vary, but key factors affecting the results are the physical fitness of the subjects, the subjects' preexercise lipid levels, and the intensity and duration of the exercise session. Also, because exercise produces an acute, delayed expansion of plasma volume after exercise, small changes in lipid concentrations can be overlooked if the results are not corrected for plasma volume. Nevertheless, the following conclusions can be made from a review of these studies.

Exercise acutely reduces TGs. This effect was first noted in 1964 when Holloszy et al. (27) described acute TG reductions in hypertriglyceridemic men, and Carlson and Mossfeldt (5) reported reductions in TGs in cross-country skiers after 8–9 h of exertion. The reduction in TGs is not immediate but occurs 18–24 h after exercise, consistent with the induction of metabolic changes, persists for up to 72 h (2,5,8–10,14,15,22,53,61,66), and is greatest in those with higher preexercise TG values (9). The effect appears to increase with energy expenditure and does not require a threshold of exertion (10) although untrained individuals may not expend sufficient calories to induce detectable changes in small studies. The most reproducible results have been obtained in fit subjects performing prolonged endurance events such as marathons.

Exercise acutely increases HDL-C. This increase has varied from 4 to 43% in various studies (2,5,8–10,14,15,22,53,61,66). The increase generally parallels the decrease in TGs in onset and disappearance, suggesting mediation by similar metabolic changes. The quality and quantity of exertion required to increase HDL-C acutely is not defined although changes in moderately fit (8,66) and well-trained (14) subjects have been reported after expenditures of 350–400 and 1000 kcal, respectively, in a single exercise session. Smaller changes may occur with less energy expenditure but require adjustments for the expansion in plasma volume (36). The increase in HDL-C in sedentary

TABLE 1. Selected studies on the acute effect of exercise on serum lipids.

Author	Subject	Mode	Intensity (% max)	Duration (min)	Kcal	Timing	TC	TG	LDL-C	HDL-C
Bounds et al., 2000 (2)	14, m, 28, t, 50.2	Treadmill running	70	77	1000	Preexercise	160	113	89	49
						IPE	−5.1*	−14.1	ns	1.6
						+24 h	0.5	−16.4*	ns	10.5*
						+48 h	−3.1	−25.9*	ns	8.1*
Crouse et al., 1997 (8)	26, m, 47, t, 42.9	Cycle ergometer	50 & 80	nr	350	Preexercise	251	163	171	46
						IPE	−3.2*	3.7	−0.6	0
						+24 h	0	−9.8	5.3*	6.5*
						+48 h	1.6*	−6.8*	4.4*	
Crouse et al., 1995 (9)	39, m, 46, ut, 31	Cycle ergometer	50 & 80	nr	350	Preexercise	254	177	173	45
						IPE	−4.7*	−5.7	−4.1	−2.2
						+24 h	1.2	−18.6*	5.8*	6.7*
						+48 h	4.7*	−14.7*	8.1*	8.9*
Davis et al., 1992 (11)	10, m, 28, t, 62	Treadmill running	50 & 75	60 min at 75% 90 min at 50%	952	−24 h	150	85	80	57
						Preexercise	ns	ns	ns	ns
						IPE	ns	ns	ns	ns
						+1 h	ns	ns	ns	ns
						+24 h	ns	ns	ns	ns
						+48 h	ns	ns	ns	ns
						+72 h	ns	ns	ns	ns
Ferguson et al., 1998 (14)	11, m, 26, t, 56.2	Treadmill running	70	59:50–111:57	800–1500	−24 h	166	101	101	45
						Preexercise	169	110	105	42
						IPE	−6.5	1	−18.1*	21.4*
						+24 h	−4.7	−36.4*	−11.4*	28.6*
						+48 h	−3	−20*	−10.5	23.8*
Foger et al., 1994 (15)	8, m, 34, t nr	Bicycle marathon	nr	711	nr	−48 h	224	132	130	67
						+24	−33*	−69*	−38*	−9
						+48	−1	−18*	−18*	33*
						+72	2	−5	−12*	34*
						+120	4	17	−3	15
						+192	1	19	−5	6
Goodyear et al., 1990 (21)	12, f, 25, t, 53	Marathon running	nr	195–270	nr	−24 h	197	49	115	72
						+10 min	−5.1	159.2*	−25.2*	5.6
						+24 h	−13.2*	2.2	−31.3*	15.3*
						+72 h	−9.1*	14.3	−13	−5.6
						+120 h	−14.7*	6.1	−18.3	−9.7
Grandjean et al., 2000 (22)	25, m, 45, ut, 33.3	Treadmill walk	70	nr	500	−24 h	217	144	147	42
						IPE	−3.2*	−2.8	−5.4	2.4
						+24 h	0.5	−11.1*	−2.0	9.5*
						+48 h	0	−11.1*	−2.7	14.3*
Hughes et al., 1991 (30)	32, f, 22, ut, 39.4	Treadmill exercise	59	15, 30, 45 min	nr	Preexercise	167	78	98	54
						+10 min	2.7	3.0	2.5	4.3
						+1 h	0	−9.6	0	2.5
						+24 h	−1.3	−18.6*	−1.0	1
						+48 h	−2.1	−21.6*	−1.0	1
Kantor et al., 1987 (36)	11, m, 33, t, 48	Cycle ergometer	80	120	nr	−24 h	197	94	126	51
						+10 min	−2.0	−14.9	−4.0*	3.9*
						+24 h	1.5	−6.4	1.0	7.8*
						+48 h	3.6*	2.1	1.6	9.8*
						+72 h	3.1	0.0	1.6	9.8*
		Cycle ergometer	80	60	nr	−24 h	195	97	136	39
						+10 min	−3.6*	6.2	−7.4*	0
						+24 h	1.0	8.3	2.2	7.7*
						+48 h	5.1*	13.4	2.9	7.7*
						+72 h	4.1*	7.2	1.5	7.7*
Sady et al. 1986 (53)	10, m, 35, t, nr	Marathon running	nr	147–236	nr	−h	197	80	118	63
						+18 h	−4	−26*	−8	10*
Visich et al., 1996 (66)	12, m, 26, t, 56.4	Treadmill exercise	74	28, 41, 55 min	400, 600, 800	−24 h	164	67	113	40
						IPE	−3.8	−14.5*	−3.1	−2.9
						+1 h	1.0	−13.2*	1.4	1
						+6 h	3.3	nr	nr	2.9
						+24 h	3.3	−13.2*	3.8	5.8*

n, subject number; gender, male (m) or female (f); age in years; training status, trained (t) or untrained (ut); and $\dot{V}O_{2peak}$ (mL · kg · min). Baseline lipids and lipoprotein-lipids are given as mg · dL, then percent change from baseline. * Significantly different from baseline, $P < 0.05$. In Crouse, 1997 LDL-C reported for 50% intensity group.

subjects appears to be due by increases in HDL3, whereas HDL2 increases in trained individuals (36). Acute changes in Apo AI and AII usually do not occur even with prolonged exertion, indicating that the acute changes in HDL-C are probably due to enhanced cholesterol delivery to the HDL particle (35,53).

Exercise acutely increases fat tolerance and LPLA (35,53). These changes have most frequently been demonstrated in fit subjects performing extreme exertion, but LPLA increases in untrained individuals exercising for as little as 1 h at 80% of maximal heart rate (36). These observations have lead to the hypothesis that exercise acutely depletes intramuscular triglycerides, which stimulates the synthesis or translocation of LPL, which hydrolyzes triglycerides from lower-density lipoproteins with transfer of the excess surface cholesterol to the HDL particle (61).

The acute effect of exercise on other enzymes involved in HDL metabolism is not established. Cholesterol ester transfer protein (CETP) transfers cholesterol from HDL to other lipoproteins. Reductions in CETP should increase HDL-C. CETP decreased in some (15), but not all, acute exercise studies (22). Lecithin cholesterol acyl transferase (LCAT) esterifies free cholesterol in the HDL particle, permitting its transport in the HDL core and an increase in cholesterol per HDL particle. LCAT has also increased acutely in some exercise studies (17) but has decreased in others (13).

Prolonged exercise generally produces small reductions in TC and LDL-C. The effect of exercise on TC is the summation of changes in the various lipoprotein subfractions so that changes in TC alone have little physiological significance. LDL-C generally decreases in trained men after prolonged exercise. This decrease is approximately 8% (53). LDL-C may also acutely decrease 5–8% in hypercholesterolemic men with exercise (8,9,22). Most of these studies estimated LDL-C using the Friedewald equation, and it is unclear whether changes in very LDL (VLDL) TG content affected the results. Furthermore, some of the reduction in LDL-C may be due to the expansion of plasma volume, which is itself a possibly beneficial acute exercise effect. Expanded plasma volume decreases blood viscosity and the concentrations of ASCVD risk factors, which may reduce their effect on the arterial wall. Exercise cessation in habitually active distance runners produced a 10% increase in LDL-C after only 2 d of inactivity that was not augmented by additional rest (63). This increase in LDL-C was accompanied by an acute decrease in plasma volume, suggesting that at least some of the lower LDL-C in endurance athletes is due to plasma volume expansion.

Summary of the acute effect of exercise on serum lipids. There is Category A evidence that endurance exercise acutely reduces triglycerides and increases HDL-C. It is likely that these changes are related to total energy expenditure, but there is insufficient evidence to define whether caloric expenditure, intensity of effort, or some combination is responsible. Exercise cessation studies confirm that the higher HDL levels in very active individuals are not due solely to an acute exercise effect. On the other hand, some of the changes in triglycerides and HDL-C that occur with brief exercise training may be largely if not entirely, an acute exercise effect. There is Category A evidence that prodigious amounts of exercise such as marathon running can acutely reduce LDL-C, but this reduction may be partly an indirect effect mediated by an acute expansion of plasma volume.

THE ACUTE EFFECT OF EXERCISE ON RESTING BLOOD PRESSURE

The reduction in resting systolic (SBP) and diastolic (DBP) blood pressure immediately after a bout of aerobic exercise was noted by Kaul et al. (40) over 30 years ago and has subsequently been termed "postexercise hypotension" (PEH) (38). An accumulating body of scientific evidence indicates that PEH is an expected physiological response to moderate-intensity dynamic exercise. PEH has been observed in normotensive and hypertensive middle-aged and older people, with the largest absolute and relative blood pressure reductions seen in hypertensive subjects (23,38). Maximal decreases in SBP of 18–20 mm Hg and DBP of 7–9 mm Hg have been reported among those with Stage I hypertension. The emergence of ambulatory blood pressure monitoring has allowed assessment of the hypotensive influence of exercise beyond the laboratory. Subsequently, it has been found that PEH may persist for up to 16 h after exercise. This offers individuals with high normal to Stage I hypertension the benefit of having their blood pressure lowered into normotensive ranges for a major portion of the day (38,48,49,59).

The acute and chronic depressor effects of dynamic exercise are a low-threshold phenomenon with hypotensive responses noted at an exercise intensity of 40% of maximum oxygen consumption (23,38,48) and after just three sessions of aerobic activity in training studies (32,43,48). The depressor influence of exercise quickly subsides with blood pressure increasing to preexercise levels after 1–2 wk of detraining (38,43). The immediacy by which PEH occurs suggests that some if not all of the hypotensive benefits ascribed to endurance training programs may be an acute postexercise phenomenon related solely to recent exercise (56).

Ambulatory blood pressure monitoring has been used to assess the effect of exercise in 8 acute and 14 exercise-training studies. The subjects were primarily white men with an average age of 44 yr who were on no medications and were sedentary and overweight to obese. The mean intensity of the exercise intervention was 65% of maximum oxygen consumption, and the duration of the typical exercise session was 38 min. In the training studies, subjects trained an average of 3 $d \cdot wk^{-1}$ for 18 wk, and maximum oxygen consumption increased a mean of 10%. Ambulatory measurements suggest that exercise training produces greater blood pressure reductions than does acute exercise (Tables 1–3). Much of this apparent effect, however, may be related to the higher preexercise pressures in the exercise-training subjects. Merely based upon the law of initial values (70), the blood pressure reductions would be expected to be larger for subjects with higher initial pressures. Consequently, the relative contribution of PEH to the blood pressure reductions of exercise training remains undefined but may be substantial in studies where blood pressure was determined within 12 h of the last exercise session.

Despite consensus that chronic exercise reduces blood pressure, multiple reports have failed to document such an effect probably because of methodological considerations (48) (Tables 1 and 2). These include insufficient sample sizes to detect the smaller decreases in blood pressure seen with ambulatory blood pressure monitoring, failure to include a control session of rest, failure to account for diurnal variation, and failure to consider the acute exercise effect of recent exercise.

TABLE 2. The mean daytime change in blood pressure after acute dynamic exercise as assessed by ambulatory blood pressure monitoring.

Author	Subjects[a]	Age (yr)	Exercise Intensity (% Maximal Oxygen Consumption)	Preexercise SBP (mm Hg)	Absolute SBP Change (mm Hg)	Relative SBP Change (%)	Preexercise DBP (mm Hg)	Absolute DBP Change (mm Hg)	Relative DBP Change (%)
Pescatello et al., 1991 (48)	6 H Men	42	55	145	−10.0	−6.9	87.00	−4.00	−4.6
Pescatello et al., 1991 (48)	6 N Men	42	55	125	2.0	1.6	74.00	1.00	1.4
Pescatello et al., 1999 (49)	7 H Women	36	60	142	−9.00	−6.3	95.00	−6.00	−6.3
Pescatello et al., 1999 (49)	11 N Women	36	60	111	2.00	1.8	72.00	1.00	1.4
Hara and Floras, 1994 (24)	14 N Mixed	30	70	136	3.00	2.2	81.00	7.00	8.6
Hara and Floras, 1994 (24)	14 N Mixed	27	70	119	1.00	0.8	66.00	9.00	13.6
Rueckert et al., 1996 (51)	18 H Mixed	50	100	150	−11.00	−7.3	101.00	−2.00	−2.0
Brownley et al., 1996 (3)	11 H Mixed	34	55	136	−6.32	−4.6	94.00	−3.80	−4.0
Brownley et al., 1996 (3)	20 N Mixed	35	55	120	−0.50	−0.4	82.00	2.90	3.5
Wallace et al., 1997 (67)	25 H Mixed	48	50	146	−5.00	−3.4	92.00	−4.00	−4.3
Wallace et al., 1997 (67)	36 N Mixed	47	50	120	1.00	0.8	73.00	0.00	0.0
Wallace et al., 1999 (68)	21 H Mixed	48	50	144	−5.00	−3.5	92.00	−4.00	−4.3
Wallace et al., 1999 (68)	25 N Mixed	50	50	120	1.00	0.8	73.00	0.00	0.0
Taylor-Tolbert et al., 2000 (59)	11 H Men	60	70	153	−6.00	−3.9	96.00	−5.00	−5.2
Mean±SD	16 ± 8	42 ± 9	61 ± 13	132.6 ± −1.3	−2.1 ± 4.6	−1.4 ± 3.3	83.0 ± 10.0	−0.3 ± 4.5	−0.2 ± 5.7

[a] H, hypertensive; N, normotensive; Mixed, men and women; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Summary of the acute effects of exercise on blood pressure. There is Category A evidence that exercise produces a acute blood pressure reduction that may persist for 12–16 h. This effect possibly contributes to the reduction in blood pressure with exercise training but is unlikely to explain it completely because most measurements in training studies are performed more than 12 h after the last exercise.

ACUTE EFFECTS OF EXERCISE ON GLUCOSE METABOLISM

There is Category A evidence that even a single session of exercise can improve glucose control in Type 2 diabetics and ameliorate insulin resistance in other subjects. This acute improvement in insulin sensitivity is short-lived and lasts for only several days. Devlin and Horton (12) found that a single session of moderate exercise lowered hepatic glucose production for the following day in patients with Type 2 diabetes. Rogers et al. (50) noted that only one week of daily exercise at 70% of $\dot{V}O_{2max}$ reduced insulin resistance in patients with Type 2 diabetes mellitus and improved glucose tolerance. A single exercise session increases the skeletal muscle's insulin sensitivity and ability to resynthesize glycogen (47), probably by increasing the muscle's number and activity of the GLUT 4 glucose transporters (28,29) and the content and activity of hexokinase (39).

We have summarized several studies that have examined the acute, dose-response effect of exercise on blood glucose control in Type 2 diabetes (Table 4) (37). In healthy nondiabetic individuals, blood glucose levels are well maintained, even during vigorous exercise. In patients with Type 2 diabetes mellitus, however, moderate-intensity exercise of approximately 45–60 min duration has been shown to lower plasma glucose by approximately 20–40 $mg \cdot dL^{-1}$ (1–2 mM) (18,34,42,44,54). The fall in blood glucose during exercise in these patients with Type 2 diabetes was remarkably similar, owing in part to the similar exercise protocols used and the level of glucose control before exercise. Only two of these studies observed no change in plasma glucose during

TABLE 3. The mean daytime change in blood pressure after chronic dynamic exercise as assessed by ambulatory blood pressure monitoring.

Author	Subjects[a]	Age (yr)	Exercise Intensity (% Maximal Oxygen Consumption)	Preexercise SBP (mm Hg)	Absolute SBP Change (mm Hg)	Relative SBP Change (%)	Preexercise DBP (mm Hg)	Absolute DBP Change (mm Hg)	Relative DBP Change (%)
Fortmann et al., 1988 (16)	42 N Men	44	65	128	−2.3	−1.8	85	−2.0	−2.4
Gilders et al., 1989 (18)	8 H Men	43	70	132	−5.0	−3.8	95	−2.0	−2.1
Gilders et al., 1989 (19)	13 N Mixed	43	70	124	−4.0	−3.2	83	1.0	1.2
Van Hoof et al., 1989 (65)	26 N Men	39	NA[b]	131	−2.0	−1.5	89	−5.0	−5.6
Blumenthal et al., 1991 (1)	31 H Mixed	46	NA	146	−3.0	−2.1	91	−1.0	−1.1
Blumenthal et al., 1991 (1)	41 H Mixed	44	70	143	2.0	1.4	90	0.0	0.0
Jennings et al., 1991 (32)	13 H Men	36	60	160	−20.0	−12.5	94	−4.0	−4.3
Jennings et al., 1991 (32)	13 H Men	36	60	160	−18.0	−11.3	94	−5.0	−5.3
Seals and Reiling, 1991 (55)	9 H Women	55	62	145	−2.0	−1.4	91	2.0	2.2
Seals et al., 1997 (56)	26 N Women	61	57	137	−3.0	−2.2	88	2.0	2.3
Somers et al., 1991 (58)	16 H Mixed	35	100	141	−5.0	−3.5	89	−8.0	−9.0
Bursztyn et al., 1993 (4)	16 H Mixed	48	55	147	1.0	0.7	91	0.0	0.0
Marceau et al., 1993 (41)	9 H Mixed	43	70	152	−16.0	−10.5	88	5.0	5.7
Wijnen et al., 1994 (69)	19 N Men	37	75	130	−1.0	−.8	83	−2.0	−2.4
Cox et al., 1996 (7)	12 N Men	42	18	131	−2.2	−1.7	81	−2.5	−3.1
Cox et al., 1996 (7)	12 N Men	42	76	138	−3.4	−2.5	84	−3.3	−3.9
Jessup et al., 1998 (33)	21 N Mixed	69	70	129	−8.0	−6.2	72	−4.0	−5.6
Moreira et al., 1999 (45)	14 H Mixed	52	60	141	−3.0	−2.1	95	−3.0	−3.2
Moreira et al., 1999 (45)	14 H Mixed	47	70	149	−7.0	−4.7	97	−4.0	−4.1
Mean ± SD	19 ± 10	46 ± 9	65.2 ± 15.9	140.2 ± 10.6	−5.4 ± 6.1	−3.7 ± 3.9	88.4 ± 6.1	−1.9 ± 3.0	−2.1 ± 3.5

[a] H, hypertensive; N, normotensive; Mixed, men and women; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[b] NA, not available.

TABLE 4. Acute exercise effects on blood glucose concentrations in Type 2 diabetes.

Citation	Subjects	Treatment	Exercise Duration	Exercise Intensity	Δ Plasma Glucose (mM)
Schneider et al., 1987 (54)	Obese Type 2 DM men (N=20)	Cycle ergometry	40 min	70–75% $\dot{V}O_{2max}$	10.3 to 9.6*
Jenkins et al., 1988 (31)	Nonobese Type 2 DM men (N=7)	Cycle ergometry	60 min	50% $\dot{V}O_{2max}$	7.9 to 7.2 (no change)
Martin et al., 1995 (42)	Nonobese Type 2 DM men (N=8)	Cycle ergometry	40 min	60% $\dot{V}O_{2max}$	10.0 to 9.0*
Minuk et al., 1981 (44)	Obese Type 2 DM men (N=4) and women (N=7)	Cycle ergometry	45 min	60% $\dot{V}O_{2max}$	11.5 to 9.5*
Kang et al., 1996 (34)	Obese Type 2 DM men (N=6)	Cycle ergometry	70 min	50% $\dot{V}O_{2peak}$	11.5 to 9.6*
			50 min	70% $\dot{V}O_{peak}$	11.5 to 9.3*
Colberg et al., 1996 (6)	Obese Type 2 DM men (N=4) and women (N=3)	Cycle ergometry	40 min	40% $\dot{V}O_{2peak}$	9.6 to 10.6 (no change)
Giacca et al., 1998 (18)	Obese Type 2 DM men (N=3) and women (N=4)	Cycle ergometry	45 min	50% $\dot{V}O_{2max}$	7.5 to 6.5*

Type 2 DM, Type 2 diabetes mellitus; $\dot{V}O_{2max}$ (peak), maximal (peak) oxygen consumption.
* Significant (P<0.05) decrease in blood glucose during exercise.

exercise (6,31). None of the participants in these studies developed hypoglycemia; in fact, all remained with elevated plasma glucose despite the exercise-induced reductions of hyperglycemia. Although not specifically addressed in these studies, it is reasonable to anticipate potentially greater decreases in blood glucose when patients are using pharmacologic agents, such as sulfonylurea drugs or insulin. A clear dose-response effect of either exercise intensity or duration on blood glucose responses in Type 2 diabetes is difficult to ascertain from the reviewed studies.

The acute effects of exercise on insulin sensitivity may relate to depletion of muscle glycogen (47) or triglycerides (46). There is regulation of muscle glycogen content so that depletion of muscle glycogen leads to enhanced glucose uptake and repletion of muscle glycogen. Kang et al. (34) compared the effect of exercise for 70 min at 50% or 50 min at 70% for 1 wk. Energy expenditures for the sessions were equivalent. After 1 wk of daily exercise, insulin sensitivity improved only when subjects exercised at 70% of $\dot{V}O_{2max}$, although changes in serum glucose levels were similar. The higher exercise intensity produced greater reductions in muscle glycogen and postexercise reductions in insulin were related to the amount of glycogen oxidized. This suggests that the short-term effects of exercise on insulin sensitivity are related to depletion of muscle glycogen and that vigorous exercise may be required to produce this acute exercise effect. Alternatively, insulin resistance is related to intramuscular triglyceride content and the acute effect of exercise on insulin resistance may be related to an exercise-induced reduction in muscle triglycerides. Pan and colleagues (46) found that among 38 nondiabetic male Pima Indians, muscle triglyceride content was inversely related to insulin sensitivity. Similarly, others have also shown an inverse relationship between muscle triglyceride content and insulin-stimulated glucose uptake (20,57). This observation suggests that vigorous exercise may not be required to produce the improvement in insulin sensitivity because free fatty acids are can be oxidized during low-level energy expenditure. Additional studies on the mechanism on how exercise affects glucose homeostasis are required before specific recommendations can be made on the intensity and duration of exercise required to acutely improve glucose control.

Summary of the acute effects of exercise on glucose metabolism. Exercise acutely reduces insulin resistance and improves glucose control, but the mechanisms and threshold required for this effect are not defined.

CONCLUSIONS

There is Class A evidence that exercise has acute effects on blood lipids, blood pressure, and glucose homeostasis. Exercise also has acute effects on other factors related to atherosclerosis, such as immunological function, vascular reactivity, and hemostasis, which are beyond the scope of this overview. Additional research is required to define the threshold of exercise required to produce these putatively beneficial effects.

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Individual differences in response to regular physical activity

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ABSTRACT

BOUCHARD, C., and T. RANKINEN. Individual differences in response to regular physical activity. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S446–S451. **Purpose:** The purpose of this review was to address the question of interindividual variation in responsiveness to regular exercise training and to define the contributions of age, sex, race, and pretraining phenotype level to this variability. **Methods:** A literature review was conducted of the studies reporting interindividual variation in responsiveness to standardized and controlled exercise-training programs, and included an analysis of the contribution of age, sex, race, and initial phenotype values to the heterogeneity in $\dot{V}O_{2max}$, high-density lipoprotein (HDL)-C and submaximal exercise, heart rate (HR), and systolic blood pressure (SBP) training responses in subjects from the HERITAGE Family Study. **Results:** Several studies have shown marked individual differences in responsiveness to exercise training. For example, $\dot{V}O_{2max}$ responses to standardized training programs have ranged from almost no gain up to 100% increase in large groups of sedentary individuals. A similar pattern of heterogeneity has been observed for other phenotypes. Data from the HERITAGE Family Study show that age, sex, and race have little impact on interindividual differences in training responses. On the other hand, the initial level of a phenotype is a major determinant of training response for some traits, such as submaximal exercise heart rate and blood pressure (BP) but has only a minor effect on others (e.g., $\dot{V}O_{2max}$, HDL-C). The contribution of familial factors (shared environment and genetic factors) is supported by data on significant familial aggregation of training response phenotypes. **Conclusions:** There is strong evidence for considerable heterogeneity in the responsiveness to regular physical activity. Age, sex, and ethnic origin are not major determinants of human responses to regular physical activity, whereas the pretraining level of a phenotype has a considerable impact in some cases. Familial factors also contribute significantly to variability in training response. **Key Words:** RESPONSE TO TRAINING, TRAINABILITY, INDIVIDUALITY, FAMILIAL AGGREGATION

We all recognize that a sedentary lifestyle is a risk factor for a number of diseases that become more prevalent with age in both genders. It is even a risk factor for premature death. In contrast, regular physical activity performed in a variety of settings is considered a behavior with favorable consequences on a large variety of health outcomes. The epidemiological, experimental, and clinical evidence for the negative effects of sedentarism and the positive influences of a physically active lifestyle will not be reviewed here. These topics have been addressed in previous consensus meetings and other relevant publications (4,10,16). The number of publications dealing with physical inactivity and activity and their effects on one or several risk factors, health outcomes, or mortality rates is already impressive and is growing. However, it is fair to say that the vast majority of the published studies have emphasized main effects and group differences while paying little attention, if any, to individual differences. It should therefore be appreciated that our present conclusions are based on the average effects observed in groups of boys and girls, men and women, or elderly subjects of both genders.

It needs to be recognized that contributions documented at the level of a group may not fully apply to each member of that group. Little is known about the individuality of the response to long-term exposure to regular exercise, to persistent sedentarism, or fluctuations with age in the level of habitual physical activity. Indeed, most of the data available have been obtained in controlled exercise studies in which subjects were exposed to regular exercise of defined mode, intensity, frequency, and duration conditions sustained for weeks or months. However, from a small body of data, we propose that there are considerable individual differences in the response to regular physical activity, at least in terms of risk factor changes, even when all members of the exercising group are exposed to the same volume of physical activity adjusted for their own tolerance level.

Because there is only a handful of studies that have specifically addressed the issue of individual differences in the response to regular exercise, an assessment of the level of evidence cannot have the same implications as for the other topics covered in the Symposium. We are of the view that, for all cases dealt with below and many others that are beyond this short review, the evidence for the presence of individual differences that are biologically meaningful is extremely strong. What is less clear is the exact nature of the mechanisms responsible for the heterogeneity in response to regular exercise. In most cases, perhaps with the exception

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of $\dot{V}O_{2max}$, the level of evidence concerning the causes of variation in responsiveness is only moderate and probably of Category B or C.

HETEROGENEITY IN RESPONSIVENESS: UBIQUITOUS AND INFORMATIVE

The first publication addressing the topic of individual differences in response to standardized exercise programs goes back only to 1983 (1). It was then emphasized that the mean response to an exercise regimen can be very misleading. For instance, a mean increase in endurance performance of, say, 25% hides the fact that some individuals may have experienced a much lower gain or no increase at all in endurance, whereas some others may have gained as much as 50% and perhaps even more. Such individual differences in trainability have been observed for any phenotype that has been investigated so far when the investigators have looked for them.

Most exercise biologists still consider the heterogeneity of scores in response to training as a nuisance. This is clearly the wrong attitude to adopt. Indeed, individual differences in the response to regular exercise are generally beyond measurement error, largely not random, and are thus informative in terms of the adaptive mechanisms involved. Individual differences for any biological phenomenon are certainly not conceived as a scourge by geneticists who have understood for a long time that biological diversity is part of the human condition and reflects in part genetic diversity.

These notions are obviously relevant to the topic of the dose-response relationship between physical activity and health. The evidence for the presence of individual differences in response to regular exercise will be reviewed with respect to four traits that relate to exercise tolerance and risk factors: maximal oxygen uptake or $\dot{V}O_{2max}$, heart rate response to a standard submaximal power output or HR 50 W, fasting level of plasma HDL cholesterol or HDL-C, and systolic blood pressure during submaximal exercise at 50 W or SBP 50 W. The review draws extensively from the HERITAGE Family Study material as it is, to the best of our knowledge, the only study to date whose goal is to address the extent and the causes of the heterogeneity in the response to regular exercise.

HETEROGENEITY OF THE $\dot{V}O_{2MAX}$ RESPONSE TO REGULAR EXERCISE

In a series of studies that we undertook 20 years ago with about 125 sedentary men and women, we were able to document the magnitude of the heterogeneity of the $\dot{V}O_{2max}$ response to standardized training programs (1,2,14). In these studies, differences in trainability could not be accounted for by age, as subjects were all young adults ranging in age from 17 to 29 yr. Sex of subjects was also not a determinant factor, as the same phenomenon was observed with the same magnitude in both young women and young men. The mean gain in $\dot{V}O_{2max}$ in these experiments was about 25% of the baseline values but with a range from no gain to a doubling of $\dot{V}O_{2max}$ (3). Similar results were subsequently reported by Kohrt et al. (9) in a group of 110 subjects, 60–71 yr of age, who trained for 9 months and more. In these older men and women, they reported a mean increase of 24%, with a range from 0 to 58%.

More extensive data on the phenomenon of individual differences in the trainability of $\dot{V}O_{2max}$ in previously sedentary men and women come from the HERITAGE Family Study (8). One should note here that considerable precautions in HERITAGE were taken to ensure that a valid and reliable measure of $\dot{V}O_{2max}$ was available before and after the exercise regimen. For instance, the baseline level is the mean of 2 $\dot{V}O_{2max}$ tests if there was less than a 5% difference between them or the highest $\dot{V}O_{2max}$ value if the difference was more than 5%. The same protocol was followed for the posttraining $\dot{V}O_{2max}$. Figure 1 depicts the enormous heterogeneity in responsiveness of $\dot{V}O_{2max}$ expressed in mL O_2 gained after being trained for 20 wk and 60 exercise sessions with a highly standardized program. The average increase reached 384 mL O_2 with an SD of 202 mL O_2. The range of response was from about zero gain to an increase of 1000 mL O_2. Figure 2 demonstrates that the same heterogeneity in response levels can be found in those who began the program with a low $\dot{V}O_{2max}$ (below the median in the left panel) and in those who were initially above the $\dot{V}O_{2max}$ median (right panel).

Table 1 (first panel) summarizes the contribution of age, sex, race, and baseline level to the trainability of $\dot{V}O_{2max}$ based on the 720 subjects who had complete data and were compliant with the training program. Age, sex, race, and baseline $\dot{V}O_{2max}$ accounted only for about 11% of the variance in the response to 20 wk of training. The sex of the subject was the largest predictor with a contribution of 5.4%, followed by age with almost 4%. In the HERITAGE Family Study, the relationship between baseline $\dot{V}O_{2max}$ and its response to the training program reached only 1% (R^2 = 0.011). Finally black and white differences were trivial, accounting for less than 1%. The

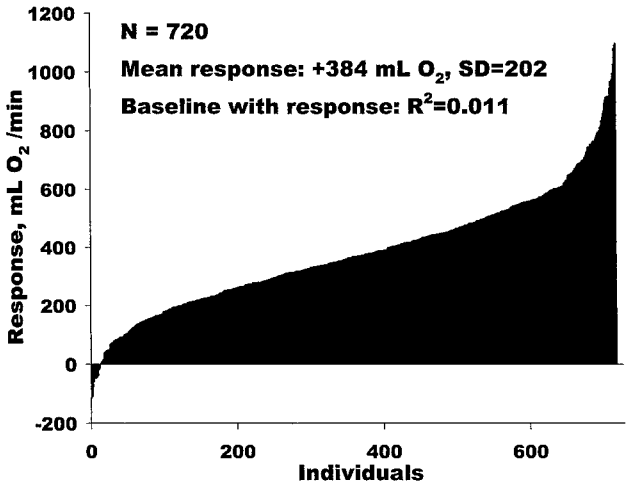


FIGURE 1—Heterogeneity of $\dot{V}O_{2max}$ training response in the HERITAGE Family Study.

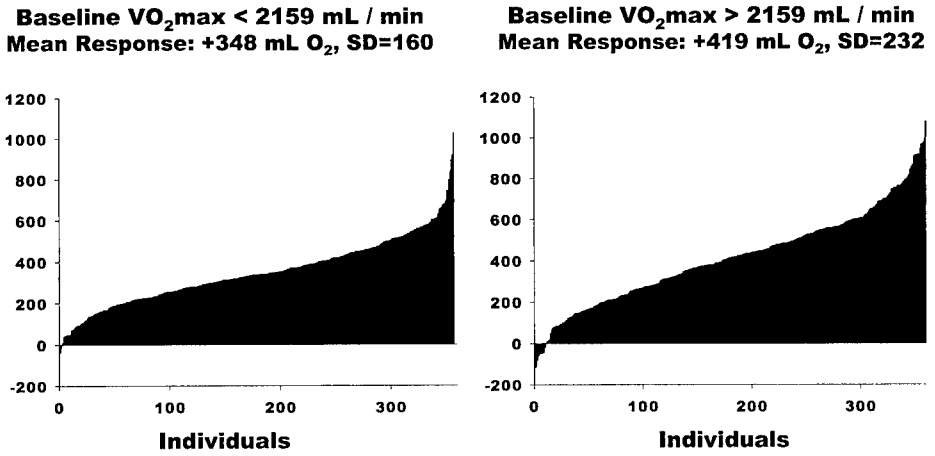


FIGURE 2—Heterogeneity of $\dot{V}O_{2max}$ training response in relation to baseline level in the HERITAGE Family Study.

reproducibility of the trait was investigated, and it was characterized by an intraclass coefficient for repeated tests of 0.97 with a coefficient of variation of 5% and no difference among the four clinical centers of the HERITAGE consortium (7,15).

In contrast, there is a strong familial aggregation for the $\dot{V}O_{2max}$ changes with regular exercise. In one study based on the HERITAGE Caucasian families, the familial aggregation was characterized by an *F*-ratio of 2.5 for the between-family variance divided by the within-family variance ($P < 0.0001$) (8).

HETEROGENEITY OF THE HEART RATE AT 50 W RESPONSE TO REGULAR EXERCISE

Figure 3 depicts individual differences in the changes in heart rate during submaximal exercise at 50 W after the 20-wk exercise program of the HERITAGE Family Study. A mean decrease of 11 beats·min^{-1} was observed among the 727 subjects with complete data. However, the SD reached 10 beats. In this particular case, the baseline level of HR 50 W was strongly and inversely related to the decrease in HR. This is exemplified in Figure 4 in which the subjects with an above-median baseline HR 50 W had a mean decrease of 16 beats·min^{-1}, SD = 10, whereas the subjects who were below the median registered a decrease of only about 7 beats·min^{-1}, SD = 8.

The contributions of sex, age, race, and baseline HR 50 W to the HR 50 W training response are summarized in Table 1 (second panel). Baseline HR 50 W levels were strongly correlated with the decrease in HR, accounting for 40% of the variance in the training-induced decreases in HR 50 W. Sex accounted for another 5%, whereas age and race were only very marginal predictors, accounting for less than 1% of the variance each. The HERITAGE reproducibility study yielded an intraclass coefficient of 0.89 with no difference across four clinical centers for the HR 50 W measurements. The coefficient of variation based on repeated tests reached 5%.

In the whole HERITAGE cohort, there was 1.8 times more variance between families than within families for the HR 50 W response to the 20-wk endurance-exercise program. The response phenotype was adjusted for age, sex, race, and baseline levels.

TABLE 1. A summary of the contributions of age, sex, race, and baseline levels to the responsiveness to regular exercise of indicators of fitness and risks in the HERITAGE Family Study.

Predictor	Partial R^2	Model R^2	F	*P*-Value
$\dot{V}O_{2max}$ training response				
Sex	0.054	0.054	40.8	0.0001
Age^3	0.016	0.069	12.0	0.0006
Age	0.007	0.077	5.6	0.018
Age^2	0.016	0.093	12.8	0.0004
Race	0.008	0.101	6.5	0.011
Baseline $\dot{V}O_{2max}$	0.011	0.112	9.2	0.003
HR 50 W training response				
Baseline HR50	0.404	0.404	490.8	0.0001
Sex	0.050	0.454	66.6	0.0001
Race	0.008	0.462	10.5	0.0012
Age	0.006	0.468	7.5	0.0062
HDL-C training response				
Baseline HDL-C	0.012	0.012	9.0	0.003
Sex	0.009	0.021	6.5	0.011
Race	0.003	0.023	2.0	0.162
Age	0.0001	—	0.1	0.791
SBP 50 W training response				
Baseline SBP50	0.317	0.317	335.3	0.0001
Sex	0.016	0.333	16.8	0.0001
Race	0.0001	—	0.1	0.709
Age	0.0000	—	0.02	0.865

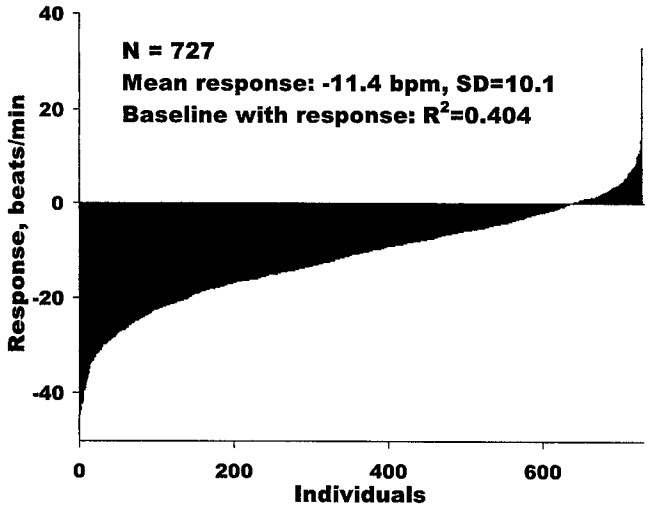


FIGURE 3—Heterogeneity of the training response of HR at 50 W in the HERITAGE Family Study.

Thus, in the aggregate, these observations indicate that there is considerable human variation in the trainability of not only maximal aerobic power but also of submaximal indicators of cardiorespiratory endurance. Even though few studies have dealt with this issue, the evidence for the presence of human heterogeneity is quite strong.

HETEROGENEITY OF THE CHANGES IN HDL-CHOLESTEROL

Surprisingly, the topic of individual differences in the response of HDL-C to regular exercise has received very little attention. Leon et al.(12), using the HERITAGE Family study data, found that heterogeneity in the responsiveness was ubiquitous among the 731 subjects who completed the training protocol and had pre- and post-training HDL-C assay results. They found that when the distribution of the percent changes in HDL-C was broken down into quartiles, the first quartile actually experienced a decrease in HDL-C of 9.3%, whereas the fourth quartile registered a mean increase of 18%. Figure 5 illustrates the extent of the HDL-C training response variation for the whole cohort. The mean increase was only 0.04 mmol·L^{-1} with SD of 0.12 (11). It is commonly accepted that HDL-C of less than 0.9 mmol·L^{-1} is clinically low. We have therefore divided the HERITAGE subjects into those with low HDL-C and those with high values. The heterogeneity in response to regular exercise within each of these two groups is depicted in Figure 6. One can observe that there were more subjects who experienced an increase in HDL-C in the clinically low group (mean increase of 0.05 mmol·L^{-1}, SD = 0.09) than in the high baseline HDL-C category (mean increase of 0.03 mmol·L^{-1}, SD = 0.13).

Table 1 (third panel) summarizes the contribution of age, sex, race, and baseline HDL-C levels to the HDL-C training response in the 731 subjects. Baseline HDL-C accounted for only 1.2% of the exercise-induced HDL-C changes, whereas sex explained almost 1%. Age and race were not significant predictors of these changes. All four variables contributed only about 2% of the variance in exercise-training-induced changes in HDL-C. Based on repeated blood samples and assays, the intraclass coefficient reached 0.94 with no difference across the four HERITAGE clinical centers. The coefficient of variation was about 6%. The *F*-ratio of the between-family variance to the within-family variance for the HDL-C changes in response to a standardized exercise regimen reached 1.8 ($P < 0.0001$) in the HERITAGE cohort.

HETEROGENEITY OF THE CHANGES IN SYSTOLIC BLOOD PRESSURE AT 50 W

To the best of our knowledge, no one has previously addressed the topic of individual differences in the regular exercise-induced changes in blood pressure. Again, we will rely on the HERITAGE Family Study data to illustrate this point. We will be using systolic blood pressure during exercise in relative steady state at 50 W as the HERITAGE subjects were generally normotensive or high normotensive in terms of resting blood pressure. We were able to retrieve a total of 723 HERITAGE subjects with valid SBP 50 W before and after training. Among these subjects, the mean decrease in SBP during cycling at 50 W was 8.2 mm Hg (SD 11.8) (Fig. 7). When the subjects were divided into two groups based on the median value of baseline SBP 50 W, those with the below-median blood pressure values

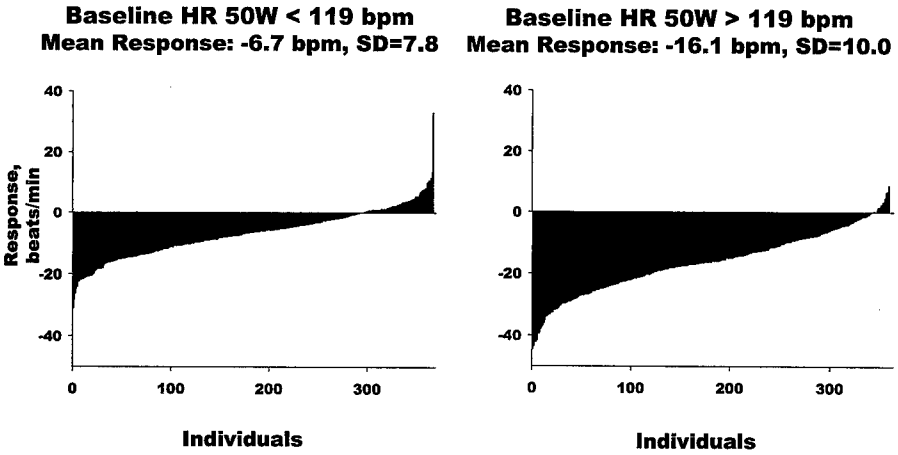


FIGURE 4—Heterogeneity of HR 50 W training response in relation to baseline in the HERITAGE Family Study.

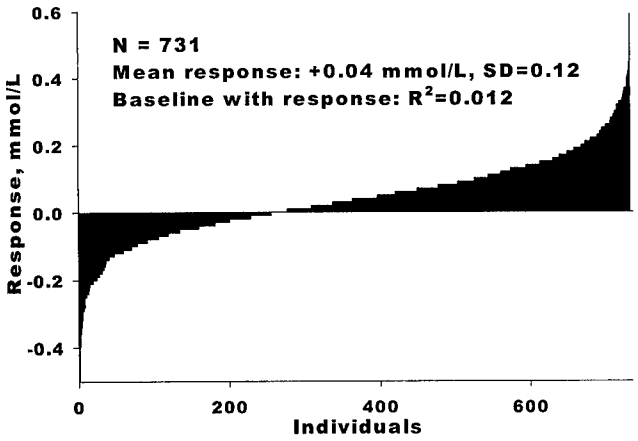


FIGURE 5—Heterogeneity of the training responses of HDL-cholesterol in the HERITAGE Family Study.

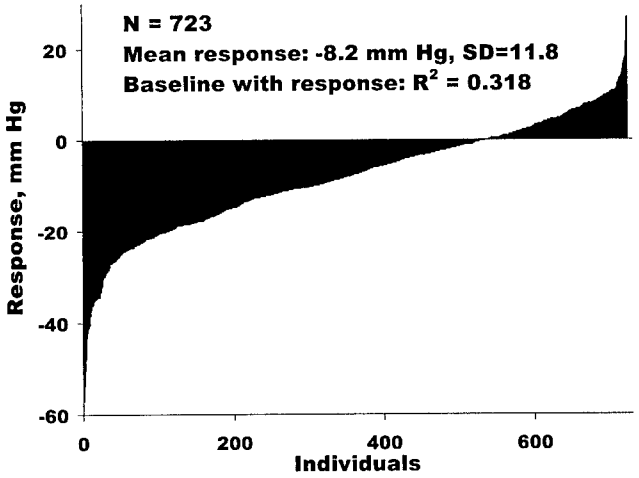


FIGURE 7—Heterogeneity of training response of SBP at 50 W in the HERITAGE Family Study.

experienced only a slight decrease of about 3 mm Hg (SD = 8.8), whereas those above median registered a decrease of 13.4 mm Hg (SD = 12.2) (Fig. 8). However, in both groups, there was considerable heterogeneity in SBP 50 W responsiveness to a standardized exercise regimen. The difference between the two groups was highly significant.

The previous results strongly suggest that the baseline level of SBP 50 W is an important determinant of its responsiveness to regular exercise. This is exactly what was found as shown in Table 1 (lower panel). Indeed, baseline SBP 50 W accounted for 32% of the variance in response, whereas sex explained 1.6%. Age and race were nonsignificant contributors to exercise SBP response to regular exercise. In HERITAGE, SBP 50 W was characterized by an intraclass coefficient for repeated assessments of 0.82 with no variation across clinical centers. The coefficient of variation reached 6%.

There was evidence of familial aggregation for the SBP 50 W response in the HERITAGE cohort with an F-ratio ranging from 1.2 to 1.4, depending on the adjustment procedures ($P < 0.02$).

CONCLUSION

The phenomenon described here is not limited to the four phenotypes selected to illustrate the point. It is ubiquitous and commonly observed. For instance, body weight and body composition changes in response to standardized experimental alterations of energy balance are characterized by considerable individual differences under both positive (6,13) and negative (5) energy balance conditions. Similar findings have been reported in a 1-yr randomized trial in both the diet and exercise arms of a study although compliance may have played a role in this case (17) compared with the other studies.

We conclude that there is strong evidence for the notion that there is considerable heterogeneity in the responsiveness of physiological indicators of risk factors to regular physical activity. Unfortunately, data are not available for indicators of morbidity or mortality rates. It is apparent from existing data that age, sex, and ethnic origin are not major determinants of human responses to regular physical activity, whereas the baseline level characteristic of a sedentary state has, in some cases, a considerable impact on the responsiveness. Human heterogeneity in response to regular physical activity is, however, not randomly distributed as it is characterized by familial aggregation.

The authors would like to express their gratitude to the colleagues of C. Bouchard involved in the early studies at Laval University (Drs. Angelo Tremblay, Jean-Pierre Despres, Louis Perusse, Marcel Boulay, Denis Prud'homme, the late Fernand Landry, the late

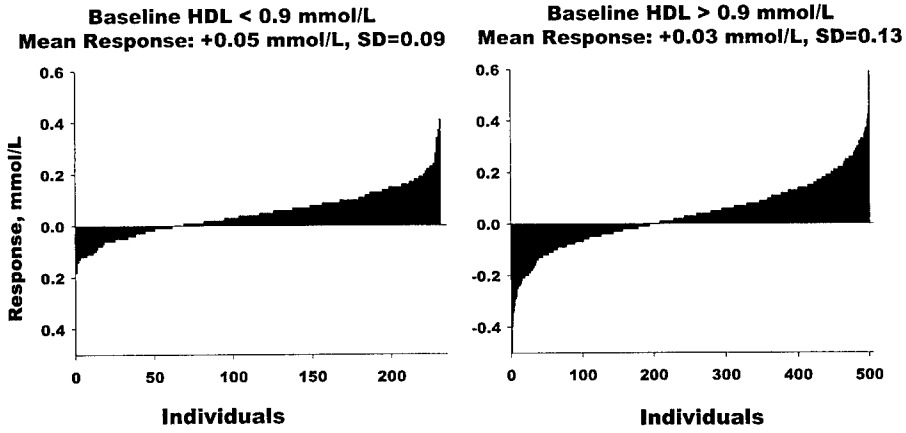


FIGURE 6—Heterogeneity of HDL-cholesterol training response in relation to baseline level in the HERITAGE Family Study.

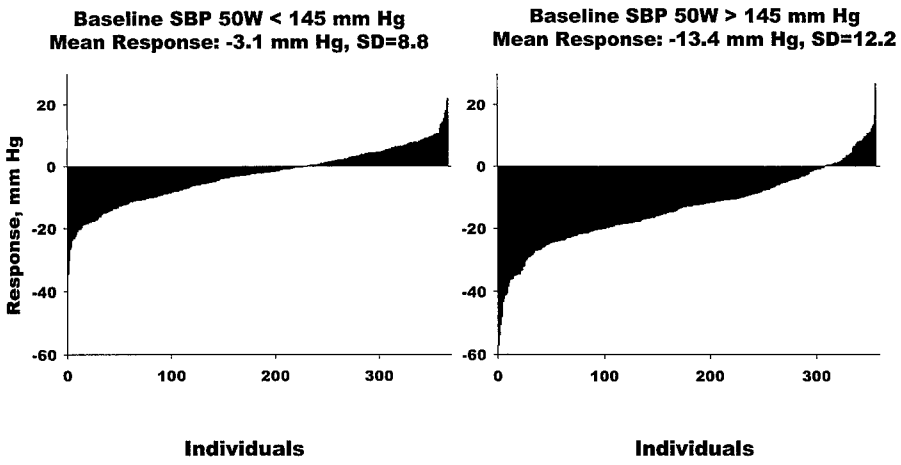


FIGURE 8—Heterogeneity of SBP 50 W training response in relation to baseline level in the HERITAGE Family Study.

Jean-Aime Simoneau, and others who were involved in these studies) and in the ongoing HERITAGE Family Study (Drs. Art Leon, D. C. Rao, Jim Skinner, Jack Wilmore, Jacques Gagnon, and several other collaborators) for their contributions. The studies of C. Bouchard on the response to exercise were supported by Fonds pour la Formation de Chercheurs et d'Aide à la Recherche, Quebec, Grant 99-ER-2449 and Natural Sciences and Engineering Research Council of Canada, Grant OPG-0042791, as well as National Heart, Lung, and Blood Institute grants (HL45670 to C.B., HL47323 to A. S. Leon, HL47317 to D. C. Rao, HL47327 to J. S. Skinner, and HL47321 to J. H. Wilmore), and the George A. Bray Chair in Nutrition.

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Chair summary and comments

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The four papers in this section concern the dose-response issue in relation to fractionalization of volume, health versus fitness outcomes, acute versus chronic effects, and individual differences in trainability. The purpose of this short summary is to recount the main findings from the four papers together with the associated level of supporting evidence and to point out the implications of these findings in relation to the dose-response issue.

Hardman (2) examined the issue of fractionalization of exercise (intermittent versus continuous exercise). Definitive information on this topic is needed to support current public policy messages that advocate accumulating short episodes of physical activity throughout the day to achieve a recommended daily total volume of physical activity. Evidence indicates that improvements in $\dot{V}O_{2max}$ are equal from long-term training programs that used one long exercise session per day versus several short exercise sessions per day for the same total duration and intensity. Moreover, the acute effect of two short sessions of moderate or hard exercise is *at least* as effective as a single session at the same total duration and intensity. On the other hand, when the total energy expenditure (volume) is equal but the *intensity* is higher, evidence from long-term training programs indicates that there are even greater increases in $\dot{V}O_{2max}$. As well, the short-term effect of a single session of moderate to hard intensity is more likely to induce a negative energy balance (weight loss) than a lighter intensity.

Oja (3) examined the relationship between the total volume of physical activity participation and indicators of health and fitness. Although the positive effect of physical activity participation on both health and fitness outcomes is already widely acknowledged, the intent was to compare the individual dose-response relationships. Evidence indicates a strong graded dose-response relationship between volume of physical activity and all-cause mortality plus several risk factors for coronary heart disease in both men and women. Also, research supports a *crude* graded dose-response relationship between volume of physical activity and $\dot{V}O_{2max}$ and a *strong* graded dose-response relationship between the intensity of physical activity and $\dot{V}O_{2max}$.

Thompson et al. (4) examined the response to acute versus chronic exercise. This paper reveals a very important methodological consideration for future investigations in which the sampling of health outcome markers must be timed to differentiate between the acute effects of the last exercise session versus the chronic effects of a long-term physical activity program. After a single session of moderate intensity physical activity, TG levels are reduced and high-density lipoprotein cholesterol levels are increased. These changes appear 18–24 h postexercise and disappear 72 h postexercise. There is an increased effect with increasing caloric expenditure. In addition, when the exercise session is prolonged and very hard, low-density lipoprotein cholesterol levels are decreased, with a graded effect for increasing caloric expenditure. After a single session of moderate intensity exercise, insulin resistance is decreased for 2–3 days, glucose control is improved in Type 2 diabetics for 2–3 days, and both systolic and diastolic blood pressures are reduced in Stage I hypertensives.

Bouchard and Rankinen (1) examined individual differences in the response to training (trainability) of health risk indicators to the same exercise program. Age, sex, and race have minimal impact on the interindividual variance in trainability. However, within members of the same family, there is significantly less variability in the response to training. In addition, in the normal population, the baseline levels of some health risk indicators have a considerable impact on the degree of trainability. For example, although the average trainability of $\dot{V}O_{2max}$ is 25%, the range is 0–50% and baseline $\dot{V}O_{2max}$ has minimal impact on this variance in trainability. To the contrary, trainability in some other health risk indicators is related to their baseline level. For example, the response to training is greater in individuals who have a higher baseline heart rate at 50 W, a higher baseline systolic blood pressure at 50 W, and a lower baseline high-density lipoprotein cholesterol level.

To summarize the implications of these four papers: 1) accumulating short episodes of physical activity is an effective method of achieving the recommended daily volume of physical activity; 2) there is a graded positive dose-response relationship between volume of physical activity and health outcomes, but the dose-response relationship between the volume of physical activity and $\dot{V}O_{2max}$ is crude; 3) an important methodological consideration in future long-term studies is the timing of sample collections to differentiate between the acute effects of the last exercise session versus the chronic effects from the entire training program; and 4) interindividual variance in the trainability of health risk indicators to the same exercise program highlights the importance of employing rigorous sampling techniques when studying the effects of physical activity participation on health outcomes.

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What to look for in assessing responsiveness to exercise in a health context

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ABSTRACT

HASKELL, W. L. What to look for in assessing responsiveness to exercise in a health context. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S454–S458. **Purpose:** When attempting to assess responsiveness to habitual exercise in a health context, there is a wide range of issues that need to be addressed in order to provide science-based recommendations for use in evidence-informed health care delivery. Issues regarding responsiveness include characteristics of the exercise regimen or dose as well as characteristics of the response or effect. **Results:** The exercise dose typically has been characterized by its type, intensity, session duration, and session frequency with the concepts of activity profile, activity volume, and accumulation over multiple bouts throughout the day recently added to these discussions. When establishing the dose for a designated outcome, specificity of the response in relation to exercise type needs to be considered. Understanding the role of intensity as a stimulus for change is critical because of the intensity-related biological responses to exercise, its role in exercise-induce medical complications, and the aversion many adults have to vigorous exercise. Receiving considerable attention is whether a higher intensity or greater volume of endurance-type exercise is more important in producing a variety of health-related benefits. To understand the potential role of accumulation of exercise, more information is needed on benefits derived from very short ($\leq$5 min) bouts of exercise performed frequently as well as very long bouts ($\geq$90 min) performed infrequently. **Conclusions:** When considering the response, it is important to establish the priority health outcomes, the relationship of the dose response for individual biological variables to the dose response for clinical outcomes, the basis for substantial interindividual variations in the response to a specific exercise dose, and the health benefit to health risk relationship for various doses of exercise. Scientific resolution of these issues will substantially facilitate the development and dissemination of appropriate guidelines for the use of exercise in promoting health. **Key Words:** HEALTH OUTCOMES, DOSE RESPONSE, VOLUME OF ACTIVITY

One approach for determining what should be established when assessing responsiveness to exercise in a health context is to consider what the requirements might be for getting exercise approved as a prescribed medication by the Food and Drug Administration (FDA) in the United States. The key features of such an approval would need to include efficacy for a specific condition, effectiveness in the target population, recommended dosing for the designated outcome, mechanisms of action, and the safety or the adverse event profile. The package insert for exercise would be quite lengthy in that there are a number of issues that would need to be considered for each of the features listed in Table 1. To address what we need to know about responsiveness to exercise in order to provide science-based recommendations for use in evidence-informed health care delivery, this manuscript will first focus on the characteristics of the exercise dose and then on the characteristics of the response or effect.

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CHARACTERISTICS OF THE EXERCISE DOSE

The major question to be asked about exercise dose is: what is the optimal dose of exercise required to produce a specific health benefit? Typically, when exercise dose in relation to health outcomes is discussed, the exercise is characterized by its type, intensity, session duration, and session frequency. Recently, the terms *activity profile*, *activity volume*, and *accumulation* have been included in these discussions. In this section, key features or issues related to each of these characteristics are summarized as they pertain to defining the health-related responsiveness to exercise.

Type of exercise. Because muscle contractions have both mechanical and metabolic properties, exercise has been classified by both of these properties, a situation that tends to cause some confusion. Mechanical classification stresses whether the muscle contraction produces movement of the limb or not: isometric (same length) or static exercise if there is no movement of the limb, or isotonic (same tension) or dynamic exercise if there is movement of the limb. A muscle contraction can either be concentric (shortening of the muscle fibers) or eccentric (lengthening of the muscle fibers). The metabolic classification involves the availability of oxygen for the contraction process and includes aerobic (oxygen available) or anaerobic (without oxygen) processes. Whether or not an activity is aerobic or anaerobic depends primarily on its intensity relative to the capacity of the muscle for that type of exercise. Most activities involve

TABLE 1. Criteria required by the FDA to approve exercise as a medicine.

Efficacy: Does it cause a specific health benefit as demonstrated by adequately designed randomized controlled trials?
Effectiveness: Is the specified benefit obtained by a reasonable percentage of the persons who undertake the prescribed regimen of exercise? Who will be the responders and who the nonresponders?
Dose: What dose of exercise provides a meaningful benefit for this specific condition? The prescribed dose needs to be defined in terms of type, intensity, frequency, and duration.
Mechanisms of Action: What changes in structure or function caused by the exercise are responsible for the specified health benefit? In a therapy such as exercise there may be multiple mechanisms for a single health benefit.
Potential Adverse Events: What are the medical risks associated with the prescribed dose of exercise? What are the medical contraindications to the prescribed exercise and what adjustments in dosing need to be made for specific populations to reduce adverse events?

both static and dynamic contractions as well as aerobic and anaerobic metabolism. Thus, activities tend to be classified based on their dominant metabolic and/or mechanical characteristics. Other classifications of exercise include endurance (aerobic) versus strength (resistance), upper versus lower body (arms versus legs), and classification by purpose (occupation, household chores, self-care, transportation, and recreational or leisure-time).

A key issue about exercise type in terms of responsiveness is the specificity of the response to a given type of exercise. Specificity refers to the fact that the biological changes that occur in response to exercise are dependent on: 1) which tissues or systems are activated or stressed by the exercise and 2) the nature of the stress placed on these tissues or systems. If this activation or stress is of appropriate intensity and amount, these tissues or systems respond favorably by increasing their capacity or efficiency (training effect). If the activation or stress is too little (not more than frequently experienced by the tissues or systems), then there is no or very little training effect or adaptation. If the activation or stress is too great, overuse injury or an unfavorable response can occur. A good example of this specificity is the increase in muscle and bone mass seen in the dominant arm versus the nondominant arm of a professional tennis player as a result of playing tennis. The response of the dominant arm to hitting thousands of tennis balls does not get transferred to the nondominant arm, which receives limited exercise. Vigorous endurance-type exercise such as running provides a major stimulus to the oxygen transport system, substrate (glycogen and fat) processing systems, and oxidative processes in leg skeletal muscle fibers, especially in slow twitch fibers. It is these systems that increase in efficiency or capacity in response to running and other endurance-type exercise. In contrast are the demands made by heavy resistance exercises, such as power lifting, that primarily activates fast twitch muscle fibers and puts stress on the body's support structures, such as bone and connective tissue. Thus, when describing responsiveness to an increase in exercise, the type of exercise needs to be accurately defined.

Intensity of exercise. The intensity of an activity can be described in both absolute and relative terms. In absolute terms, it is either the magnitude of the increase in energy required to perform the activity (aerobic or endurance exercise) or the force produced by the muscle contraction (resistance or strength exercise). The increase in energy is usually determined by measuring the increase in oxygen uptake, which is expressed in units of oxygen or converted to a measure of heat (kcal) or a measure of energy expenditure (kJ). The force of the muscle contraction is measured by how much weight is being moved or the force exerted against an immovable object and expressed in kilograms or pounds. In relative terms, the intensity of the activity is expressed in relation to the capacity of the person performing the activity. For energy expenditure, the intensity usually is expressed as a percent of the person's aerobic power (percent of maximal oxygen uptake). Because there is a linear relation between the increase in heart rate and the increase in oxygen uptake during dynamic exercise, percent of maximal heart rate, or heart rate reserve (maximal heart rate minus resting heart rate) is also used as an expression of exercise intensity relative to the person's capacity. For muscle force, the relative intensity of the contraction is expressed as a percent of the maximal force that can be generated for that activity (percent of maximal voluntary contraction or percentage of one repetition maximum) (see Table 1 in consensus panel report and contribution by E. Howley for further discussion).

Intensity is a key factor in the discussion regarding the responsiveness to exercise for achieving health outcomes. Not only does intensity play a major role in producing the favorable adaptations to exercise, but it also has a major role in the various health risks produced by increases in exercise. As stated in the section on type of exercise, adaptations occur when the exercise stimulus to a specific tissue or system is greater than that usually experienced. Thus, for a person who habitually walks at 4.8 $km \cdot h^{-1}$ (3 mph) for 2 miles, an increase in walking speed (intensity) to 6.4 $km \cdot h^{-1}$ (4 mph) will stress the oxygen transport system, substrate (glycogen and fat) processing systems, and oxidative processes in leg skeletal muscle fibers producing adaptations in these systems. Once adaptations have been made to this intensity of exercise, increases in intensity will be needed to produce additional intensity-dependent adaptations.

Key issues regarding the role of intensity in defining responsiveness to exercise include the following: 1) how intensity is expressed (absolute versus relative to capacity); 2) agreement on intensity classification for specified exercises; and 3) for which health-related responses is an increase in exercise intensity a critical stimulus. In most experimental studies evaluating the effects of increased exercise on various biomarkers of health, the intensity is expressed relative to each person's capacity. However, in most, if not all, prospective observational studies, exercise intensity is expressed in absolute terms (no adjustment made for each person's exercise capacity). These differences in methodology prevent direct comparison of dose-response data from these two major sources of information. There have been major attempts to standardize the assignment of intensity to various activities (1) and to classify activities into various intensity categories (light, moderate, heavy, etc.) (2). However, there still are meaningful differences in

the classification of such activities as walking at 3.5 mph or what walking speed is meant by brisk walking. Standardization of these classifications is essential for establishing the relationship between intensity and health outcomes. For some outcomes, it appears that the total amount of exercise performed is more important than at what intensity (above some minimal level) the exercise is performed (6). Establishing which outcomes can be achieved at lower exercise intensities is important in helping convert exercise guidelines from less of a medical model to more of a public health model.

Session duration and frequency. Session duration and frequency have traditionally been considered when prescribing an exercise plan that focuses on performing a discrete bout of exercise three or more times per week (2). For enhancing cardiorespiratory function and for cardiovascular disease prevention and rehabilitation, session duration of 20–60 min of moderate to vigorous intensity endurance-type exercise performed three or more days per week has been the typical recommendation. However, the recent adoption of the concept of accumulating exercise over multiple short bouts (8–10 min) during the day has created a number of unanswered questions about session duration and frequency when performing endurance-type exercise. When performing resistance exercise, duration is not measured in time but by the number exercises performed, the number of sets per exercise, and the number of repetitions per set.

Key issues regarding the role of session duration and frequency in responsiveness include: 1) how short can a bout of endurance-type exercise be and still contribute to specific health outcomes (e.g., does stair climbing for 1 min per session 20 times per day provide benefits similar to a single session per day of 20 min?); 2) do sessions of long duration (>90 min) on 1 or 2 d per week provide similar benefits as 30-min sessions performed 5–6 d per week; and 3) do multiple short bouts of exercise spread throughout the day provide more benefit than a single longer bout of equal amount resulting from repeated acute effects of exercise on specific health outcomes?

Accumulation of exercise over the day. The concept of accumulation of exercise by performing multiple short bouts (8–10 min each) throughout the day was first included in major guidelines in 1995 (8). These recommendations were based on some indirect data from prospective observational studies relating activity level to coronary heart disease (CHD), cardiovascular disease and all-cause mortality and on results of three experimental studies that evaluated the effects of a single longer bout per day versus 3–4 shorter bouts per day (total exercise performed held constant) on aerobic capacity, plasma high density lipoprotein (HDL)-cholesterol concentration, and body weight. These data indicated that performing multiple short bouts of moderate to vigorous activity produced results not too dissimilar to those produced by the longer bouts. Additional evidence has been reported that supports these initial results (10).

If the accumulation concept is valid, it is then important to consider the role of the volume of exercise in responsiveness. Volume is the product of exercise intensity, duration, and frequency usually expressed in some units of energy expenditure (e.g., kcal, MET min). If the key stimulus for health benefits is exercise volume above some minimal intensity threshold, then a wide variety of exercise profiles can be encouraged for promoting health (7). In Figure 1, four different exercise profiles are depicted that provide a similar exercise volume expressed in total energy expended. These various profiles of exercise, if valid, provide a wide range of opportunities for achieving an adequate volume dose.

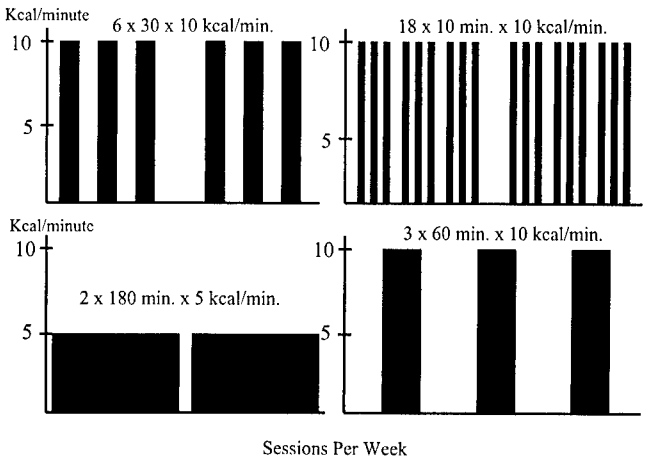


FIGURE 1—Different approaches to performing a given volume of exercise (1800 kcal·wk^{-1}) by varying intensity, session duration, and session frequency. Intensity is expressed in kilocalories per minute and volume in kilocalories per week.

Key issues regarding the role of accumulation or volume include: 1) the health benefits produced by accumulating 30 or more minutes of exercise per day performing multiple short (≤5 min) bouts of moderate intensity exercise; 2) whether multiple short bouts of exercise versus one longer bout per day produce more favorable acute responses; and 3) what are the limits of the accumulation approach in terms of the minimum duration of each exercise session. Also, there needs to be developed motion and/or physiological monitoring systems that will accurately document the exercise profile over five or more consecutive days with acceptable subject and staff burden.

CHARACTERISTICS OF THE EXERCISE RESPONSE

The major questions to be asked about the exercise response include: 1) what are the key health-related responses for which a required exercise dose is desired; 2) how does the exercise dose that produces changes in individual biological benefits relate to a clinical benefit: 3) what are the basis for substantial interindividual variations in the response to a specific exercise dose; and 4) what is the health benefit to health risk relationship for various doses of exercise?

Key responses. Our attempts to date in trying to establish the required dose of exercise to achieve specific clinical benefits have been substantially hampered by not knowing what changes at the cellular or subcellular level are

responsible for most specific health outcomes. Because of this lack of knowledge, we are somewhat shooting in the dark when attempting to determine the dose of exercise required by looking at changes in biomarkers or risk factors rather than at changes in gene expression or protein synthesis. For example, if we knew which genes were activated by exercise to produce a reduction in resting blood pressure, we might be able to use this information to better establish the dose of exercise that leads to a reduction in hypertension.

When trying to answer the question, how much exercise is enough, the specific outcome of interest has to be taken into account due to the specificity of the exercise effect. Substantial data exist demonstrating that the dose-response relationship varies widely for different outcomes. For example, the stimulus for changes in fat and carbohydrate metabolism is most likely to be responsive to increases in total energy expenditure above some intensity threshold, whereas changes in bone density are likely due primarily to the stress placed on bone by forces working against gravity or by vigorous muscular contraction. Also, the characteristics of the person, such as age, gender, body composition or size, diet, smoking status, use of medications, clinical status, and baseline exercise and fitness levels, may substantially influence the dose-response relationship for exercise and health-related outcomes.

Multiple biological changes may produce a specific clinical benefit. For some clinical conditions such as CHD, it appears that there are a number of exercise-induced biological changes that contribute to a reduction in morbidity and mortality. These changes include, but are not limited to, improvements in the plasma lipoprotein profile, a decrease in insulin resistance, reductions in blood pressure, increased coronary blood flow, and decreases in myocardial oxygen demand. It is likely that the dose-response relationship varies among these biological changes and the dose-response relationship for CHD clinical events is some integration of the dose-response relationship for all of the biological mechanisms. Thus, the dose-response relationship for any one biological variable does not necessarily represent the dose-response relationship for a reduction in CHD clinical events. This concept is presented in Figure 2, where hypothetical dose-response curves for selected biological changes that appear to contribute to a reduction in CHD mortality are displayed along with the dose response for CHD mortality.

Key issues include knowing how the dose-response relationships for specific biological risk factors relate to the dose-response relationship for clinical outcomes such as myocardial infarction, stroke, noninsulin dependent diabetes mellitus, and site-specific cancers. All of these major clinic entities are likely to benefit through a variety of exercise-induced biological changes. This goal will be facilitated by research that establishes which biological changes most contribute to the reduction in risk for these clinical conditions.

Acute versus chronic effects. When attempting to define the dose response for the health benefits of exercise, it is useful to consider that some effects may occur as an

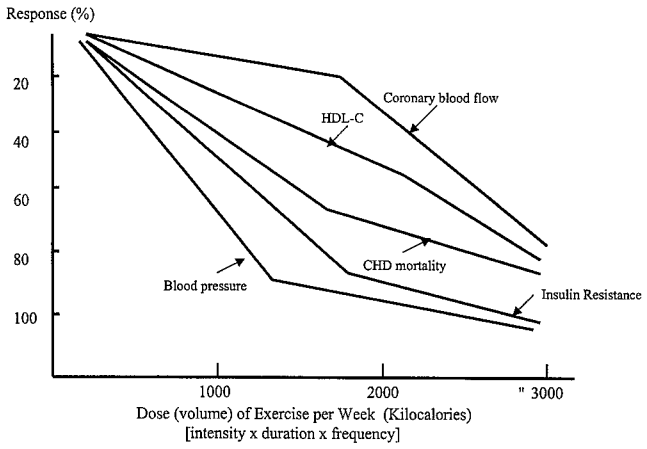


FIGURE 2—The dose-response relationship for exercise induced changes in selected CHD risk factors and CHD. The dose is expressed as volume of exercise in kilocalories per week. The dose response relationship is hypothetical and not based on published data.

acute response to a single or several bouts of exercise, some only as a training response, and some as the result of an interaction between acute and chronic training responses. An example of an acute response is that a 45-min bout of stationary cycling at 70% of $\dot{V}O_{2max}$ by older men and women with moderate hypertension significantly decreases systolic blood pressure for up to 3 h post exercise (5). Also, it has been demonstrated that in hypertriglyceridemic men, fasting plasma triglyceride concentration the morning after a 45-min bout of exercise at approximately 75% of aerobic capacity is lower than when such exercise is not performed (4). Over a 5-d period, if exercise is performed every day, fasting triglyceride concentration decreases further the following day. Thus, this acute response is augmented by repeated bouts of exercise. This reduced triglyceride concentration is rapidly reversed if the exercise is not performed for several days. This could be called an augmented acute response in that there is no further decrease even after weeks of exercise on a regular basis. It is likely that as a person's physical working capacity increases and the absolute intensity of exercise performed during an exercise session is increased (relative intensity stays the same), the acute responses of various physiologic or biochemical reactions will be enhanced (a more fit person is able to expend more energy during a set period of time). This would be true for any benefit directly tied to the magnitude of energy expended during the exercise session.

Key issues include 1) establishing the acute responses to exercise of various exercise intensities and durations for biological measures which contribute to an improvement in clinical status; 2) evaluating the differences in acute responses when the exercise session is performed at different times in relation to meals; and 3) determining the interaction between acute and chronic (training) responses for selected biological variables.

Interindividual variations in response to a specific exercise dose. Typically, the results of a randomized controlled trial evaluating the effects of exercise training on a specific health-related outcome are presented

comparing the mean change in the exercise group versus the mean change in the control group. When the mean change in the exercise group is greater than the mean change in the control group, then that dose is said to be efficacious in producing the specific outcome. However, there can be substantial variation in the change among the subjects in the exercise group exposed to the same exercise stimulus, with some subjects having no change or even a decrease whereas other subjects have changes much greater than the mean. It is apparent that much of this variation in response can be due to individual biological variation and is not due to measurement error. A good example of this interindividual variation in the response to a set exercise regimen was reported by Dionne and colleagues (4) for changes in maximal oxygen uptake among 46 healthy young men in response to endurance exercise training performed three times per week for 24 wk. They reported a range in the change in maximal oxygen uptake from 0.06 to 1.03 $L \cdot min^{-1}$ with the mean change being 0.51 $L \cdot min^{-1}$. Thus, although the mean increase in maximal oxygen uptake was significant, the dose was ineffective for some subjects and highly effective for others.

A key issue for the future would be to include in the report of exercise training studies some expression of the individual variation in responses to the training as well as the mean and standard deviation. Also, it would be valuable to know how many subjects in the exercise group exceeded a prespecified level of change (e.g., 75% of subjects had an increase in their HDL-cholesterol of $\geq$ 5 $mg \cdot dL^{-1}$). Also, a more systematic investigation is needed of personal characteristics, genetic and nongenetic, which influence the interindividual variation in dose response for specific health and performance outcomes.

Health benefits to health risks relationship. With regard to health status, exercise can be a two-edged sword. As the intensity and amount of exercise performed is increased, the greater the risk that injury will occur, especially musculoskeletal problems for most individuals and cardiovascular complications in those people already with underlying disease. Of particular concern when attempting to establish the optimal dose of exercise for health outcomes is intensity because it is the major contributor to exercise-induced medical complications. Thus, the dose-response assessment needs to consider not only what dose induces the greatest health benefit, it also needs to consider the risk profile for that dose. It may be that higher exercise intensity (running) will provide greater benefit for a specific biological outcome but that a moderate intensity exercise (brisk walking) will provide the best overall health benefit in at-risk populations because of its lower risk profile (3). This concept is depicted in Figure 1 of the consensus panel report.

Key issues include: 1) establishing the risk profile for various exercise regimens in different populations, especially in older persons (9); 2) documenting doses of exercise that can provide benefit at minimal risk in selected at-risk populations; and 3) developing algorithms for predicting risk posed by different exercise regimens for specific populations.

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Physical activity and all-cause mortality: what is the dose-response relation?

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ABSTRACT

LEE, I-M., and P. J. SKERRETT. Physical activity and all-cause mortality: what is the dose-response relation? *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S459–S471. **Purpose:** The purpose of this review is to assess the dose-response relation between physical activity and all-cause mortality. We examined these parameters of physical activity dose: volume, intensity, duration, and frequency. **Methods:** We used a computer-assisted literature search to identify papers on this topic. After excluding papers examining only two levels of physical activity or fitness, papers investigating specific causes of mortality, reviews, and those not written in English, 44 papers satisfying all criteria were included in this review. **Results:** There is clear evidence of an inverse linear dose-response relation between volume of physical activity and all-cause mortality rates in men and women, and in younger and older (≥60 yr) persons. Minimal adherence to current physical activity guidelines, which yield an energy expenditure of about 1000 kcal·wk^{-1} (4200 kJ·wk^{-1}), is associated with a significant 20-30% reduction in risk of all-cause mortality. Further reductions in risk are observed at higher volumes of energy expenditure. It is unclear whether a volume of <1000 kcal·wk^{-1} also may be associated with lower risk; there are some data supporting this. Due to limited data, it is also unclear whether vigorous-intensity activity confers additional benefit beyond its contribution to volume of physical activity when compared with moderate-intensity activity. No data are available on duration and frequency of physical activity in relation to all-cause mortality rates after controlling for volume of physical activity. **Conclusions:** All studies in this review are observational studies, so conclusions are based on Evidence Category C. There is an inverse linear dose-response relation between volume of physical activity and all-cause mortality. Further research is needed to clarify the contributions of its components—intensity, duration, and frequency—to decreased all-cause mortality rates. **Key Words:** CARDIORESPIRATORY FITNESS, DEATH, EPIDEMIOLOGY, EXERCISE, PHYSICAL FITNESS

The hypothesis that physical activity and physical fitness promote health and longevity is not new. As far back as 2500 BC in ancient China, we find records of organized exercise for health promotion (28). Today, there is clear evidence to support this hypothesis (48). What is less clear is the shape of the dose-response relation between physical activity or fitness and all-cause mortality rates. Clarifying this relation is important in light of a widely cited and heavily promoted recommendation (33,37,48) that calls for at least 30 min of moderate-intensity physical activity (e.g., brisk walking at 3–4 mph) on most days of the week. We refer to this as the "current" recommendation. It contrasts with previous recommendations that advocated vigorous-intensity exercise (e.g., jogging or running) for at least 20 min continuously three times a week (1).

Although the volume of energy expended by minimal adherence to current or previous recommendations is similar (on the order of 1000 kcal·wk^{-1} [4200 kJ·wk^{-1}]), two major differences exist between the current and previous recommendations. They are: 1) the current emphasis on moderate, rather than vigorous, activity; and 2) the current allowance for the accumulation of short sessions of activity, instead of one longer, continuous session. These concessions were made partly to encourage physical activity among sedentary individuals because the previous, more difficult prescription was believed to pose a barrier (48). With the high prevalence of sedentary behavior today, it is important to ascertain the minimum dose of physical activity required to decrease all-cause mortality rates. From a public health perspective, advocating small (effective) doses of physical activity is likely to be more palatable to the many physically inactive persons.

The purpose of this review is to describe the shape of the dose-response curve between physical activity or fitness and all-cause mortality. Because of the large number of sedentary individuals, we are particularly interested in the minimum dose of physical activity required to decrease all-cause mortality rates. In the broadest sense, "dose" can be defined as the volume of physical activity. We also will examine the parameters that characterize volume of physical activity: intensity, frequency, and duration. The specific questions we will address are:

1. What are the available data for a dose-response relation between physical activity or fitness and all-cause mortality rates?

2. What is the minimum *volume* of physical activity associated with decreased all-cause mortality rates? With increasing dose, do mortality rates decline commensurately, or is there a threshold effect (i.e., an L-shaped curve)?

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3. What is the minimum *intensity* of physical activity associated with decreased all-cause mortality rates? Holding the volume of physical activity constant, do mortality rates decline commensurately with increasing intensity, or is there a threshold effect?

4. Holding the volume of physical activity constant, what is the minimum *duration* of physical activity associated with decreased all-cause mortality rates? With increasing duration, do mortality rates decline commensurately, or is there a threshold effect?

5. Holding the volume of physical activity constant, what is the minimum *frequency* of physical activity associated with decreased all-cause mortality rates? With increasing frequency, do mortality rates decline commensurately, or is there a threshold effect?

METHODS

We used a computer-assisted literature search to identify papers published between 1966 and July 2000 by using the National Library of Medicine's Medical Subject Heading (MeSH) keywords related to physical activity (physical fitness, exercise, physical education and training, exertion, sports, running, walking, recreation, and leisure activities) and all-cause mortality (mortality and death). We excluded papers examining only two levels of physical activity or fitness, because this would not allow assessment of a dose-response relation, papers investigating only specific causes of mortality, review papers, and papers not written in English, because we did not have the means to translate them. We also checked the reference list of papers for additional papers not identified by the computerized literature search. By these means, we identified 44 papers. Both authors reviewed each of these papers, which are summarized in Table 1.

RESULTS

Of the 44 papers identified, the majority investigated physical activity. Five studies assessed physical fitness (6,10,39,41,45), whereas two assessed both activity and fitness (14,49). For this review, we have assumed equivalence between physical activity and physical fitness, because regular physical activity improves physical fitness. Moreover, from a practical perspective, public health recommendations target physical activity, a behavior, rather than physical fitness, an attained physiologic condition. Of the 38 papers examining physical activity, most assessed only leisure-time physical activity (LTPA), three assessed only occupational physical activity (OPA) (7,29,32), and nine assessed both LTPA and OPA (2,3,8,15,31,40,42,43,51).

Evidence for a dose-response relation. The primary parameter analyzed in the 44 studies was volume of physical activity (see below). There was evidence of an inverse linear dose-response relation between physical activity (or fitness) and all-cause mortality rates: 34 of the 44 studies showed an apparent dose-response relation in at least one subgroup (Table 1). A formal test of linear trend was conducted in only 17 studies, with 15 reporting a statistically significant inverse linear trend in at least one subgroup of subjects (Table 1).

Volume of physical activity. All 44 papers assessed the relation between volume of physical activity (or fitness) and all-cause mortality rates. Several investigators estimated energy expenditure, whereas others used proxies of energy expenditure (Table 1). These proxies included ordinal groupings, quantiles of physical activity, frequency of physical activity, and duration of physical activity.

As described above, 34 of the 44 studies reviewed showed an apparent inverse linear dose-response relation between volume of physical activity and all-cause mortality rates in at least one subgroup of subjects (Table 1). Of the remaining 10 studies, five noted a threshold effect, with a decline in all-cause mortality rates between the least active and second least active group but no diminution of rates at higher levels of physical activity (i.e., an L-shaped curve) (9,25,26,40,49). The other five reported no significant association between physical activity and all-cause mortality rates (15,19,20,29,52).

For a more stringent evaluation of the dose-response relation, we examined only studies that formally tested for a significant linear trend of declining all-cause mortality rates with increasing volume of physical activity (or fitness). This formal test was carried out in 17 studies; 15 observed significant, inverse linear trends in at least one subgroup (3,4,6,8,11–14,17,18,21,22,34,35,39), whereas two reported no significant trend (15,20).

An inverse linear dose-response relation between volume of physical activity and all-cause mortality rates was observed in both men and women. Of the 44 studies, 20 included men and women, 20 included men only, and 4 included women only. Of the 24 that included female subjects, 20 presented findings specifically for women (2,4,6,8,14–19,27,30,31,38,39,42,43,49,51,52). Findings for women generally paralleled those for men (Table 1).

The ages of subjects in most of the studies spanned a wide range, from young adulthood to old age. In 10 studies, results for adults aged 60 yr and older were presented separately (2,3,13,19,20,26,31,38,43,47). All but two (19,20) showed apparent linear inverse dose-response associations (i.e., formal statistical tests for trend were not always carried out) between volume of physical activity and all-cause mortality rates. In the Seventh-day Adventist Study, a significant benefit of physical activity was observed up to attained age of 80 yr (26).

Few studies quantified volume of physical activity in a manner that allows for direct translation to public health recommendations. Statistically significant decreased all-cause mortality rates occurred during follow-up among subjects who expended >1000 kcal·wk^{-1} (22,34), >980 kcal·wk^{-1} (11), an average of 518 kcal·wk^{-1} (25), >500 kcal·wk^{-1} (35); walked 1–2 miles·d^{-1} (13); or who exercised moderately or vigorously at least a few times a month to once a week (18). Risk reductions on the order of 20–30% were observed. This suggests that minimal adherence to either the current or previous physical activity guidelines,

TABLE 1. Summary of epidemiologic studies on the dose-response relation between physical activity or fitness and all-cause mortality.

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Andersen et al., 2000, Denmark (2)	3 prospective cohorts, 17,265 men and 13,375 women aged 20–93 yr	14.5 yr; 8549	4 levels of LTPA and OPA in the previous year, assessed by questionnaire	vs inactive LTPA Light: RR = 0.68 (0.64–0.71) Moderate: RR = 0.61 (0.57–0.66) Heavy: RR = 0.53 (0.41–0.68) Among subjects with light, moderate, and heavy LTPA, sports participation in men: RR = 0.63 (0.51–0.79) in women: RR = 0.47 (0.34–0.66) OPA: inverse association in women, no association in men.	Adjusted for age and sex. Adjustment for chronic disease did not change findings. Inverse association observed for individuals aged 20–44, 45–64, and ≥65 yr, and in men and women.
Bijnen et al., 2000, The Netherlands (3)	Prospective cohort (Zutphen Elderly Study), 472 Dutch men aged 70–90 yr	5 yr; 118	Physical activity assessed by questionnaire in 1985 and 1990 asking about walking, bicycling, hobbies, odd jobs, and sports, converted to a "total physical activity" score	vs lowest tertile (T1) of activity in 1990 T2: RR = 0.56 (0.35–0.89) T3: RR = 0.44 (0.25–0.80) *P* for trend, <0.01 Bicycling, but not gardening, walking, or other activities, showed an inverse association with mortality. Changing from an active to a sedentary lifestyle between 1985 and 1990, compared with remaining active: RR = 1.72 (1.04–2.85).	Adjusted for age, disease, functional status, and lifestyle factors.
Lee and Paffenbarger, USA (22)	Prospective cohort (Harvard Alumni Health Study), 13,485 men, mean age 57.5 yr, free of CVD, COPD, and cancer	15 yr; 2539	LTPA energy expenditure derived from questionnaire asking about walking, stair climbing, and sports/recreation	vs <4200 kJ·wk^{-1} in LTPA: 4200–<8400 kJ·wk^{-1}: RR = 0.80 (0.72–0.88) 8400–<12,600 kJ·wk^{-1}: RR = 0.74 (0.65–0.83) 12,600–<16,800 kJ·wk^{-1}: RR = 0.80 (0.69–0.93) ≥16,800 kJ·wk^{-1}: RR = 0.73 (0.64–0.84) *P* for trend, <0.001 *P* for trend: across categories of walking, 0.004 across categories of stair climbing, <0.001 across categories of light (<4 METs) sports/recreation, 0.72 across categories of moderate (4–<6 METs) sports/recreation, 0.07 across categories of vigorous (≥6 METs) sports/recreation, <0.001	Adjusted for age, BMI, smoking, alcohol use, and early parental death. Analyses of each of the components of LTPA simultaneously adjusted for the other components of LTPA, in addition to the variables above.
Stessman et al., 2000, Israel (47)	Prospective cohort (Jerusalem 70-Year-Olds Longitudinal Study), 456 men and women born in 1920–21	6 yr; 240	4 levels of LTPA at baseline—no exercise (walks less than 4 h weekly), moderate activity (walks approx. 4 h weekly), sports participation at least twice weekly, and regular activity (walks at least 1 h a day)	vs no activity: Moderate: RR = 0.41 (0.19–0.91) Sports: RR = 0.73 (0.33–1.62) Regular: RR = 0.14 (0.04–0.50)	Adjusted for sex, smoking, subjective economic hardship, and preexisting medical conditions.
Dorn et al., 1999, USA (8)	Prospective cohort (Buffalo Blood Pressure Study), 698 men and 763 women aged 15–96	29 yr; 578	LTPA and OPA assessed by 28 questions regarding time spent sleeping, sitting, driving, standing, carrying or lifting, walking, gardening, exercising, and playing sports.	For every 1 kcal·kg^{-1}·h^{-1} of physical activity, men: Nonobese: RR = 0.55 (0.36–0.84) Obese: RR = 1.44 (0.86–2.43) No significant association seen in women.	Adjusted for age, education, smoking, and mean arterial blood pressure.
Erikssen et al., 1998, Norway (10)	Prospective cohort, 1428 healthy men aged 50–70 yr	13 yr; 238	Physical fitness determined by bicycle test in 1972–75 and 1980–82	vs lowest quartile (Q1) in 1980–82: Q2: RR = 0.72 (0.52–0.99) Q3: RR = 0.48 (0.33–0.71) Q4: RR = 0.45 (0.29–0.69) Regardless of baseline level of fitness, improved fitness over 5–10 yr resulted in decreased all-cause mortality rate.	Adjusted for age, systolic blood pressure, heart rate, lipids, BMI, physical activity, and smoking status.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Fried et al., 1998, USA (11)	Prospective cohort (Cardiovascular Health Study), 5201 men and women aged ≥65 yr	5 yr; 646	Kcal/week in moderate or vigorous LTPA estimated from interview	vs ≤67.5 kcal·wk^{-1} >67.5–472.5: RR = 0.78 (0.60–1.00) >472.5–980: RR = 0.81 (0.63–1.05) >980–1890: RR = 0.72 (0.55–0.93) >1890: RR = 0.56 (0.43–0.75) *P* for trend, <0.005	Adjusted for age, smoking, BMI, and numerous other factors, including alcohol use, blood pressure, serum cholesterol, and chronic diseases.
Hakim et al., 1998, USA (13)	Prospective cohort (Honolulu Heart Study), 707 physically capable, nonsmoking men aged 61–81 yr	12 yr; 208	Daily distance walked	vs <1 mile·d^{-1} 1.0–2.0: RR = 0.68 2.1–8.0: RR = 0.59 *P* for trend, 0.002	Adjusted for age.
Kujala et al., 1998, Finland (17)	Prospective cohort (Finnish Twin Cohort), 15,902 men and women aged 25–64 yr free of various chronic diseases	18 yr; 1253	3 levels of LTPA plus calculated MET index assessed by questionnaire on activity, frequency, duration, and intensity	vs sedentary Occasional exercisers: RR = 0.80 (0.69–0.91) Conditioning exercisers: RR = 0.76 (0.59–0.98) vs lowest MET quintile (Q1) Q2: RR = 0.85 Q3: RR = 0.72 Q4: RR = 0.68 Q5: RR = 0.60 *P* for trend, 0.04 Participation in vigorous activities, RR = 0.79 (0.56–1.10)	Adjusted for age, sex, smoking, occupation, and alcohol use. Inverse association observed for men and women. Inverse association remained after taking into account genetic factors (twin status).
Roger et al., 1998, USA (39)	Retrospective cohort (Olmsted County), 1452 men, mean age 47 yr, and 741 women, mean age 51 yr, referred for treadmill testing	6.3 yr; 123	Physical fitness determined by maximal exercise test on treadmill	For each 1 MET increase in workload men: RR = 0.80 ($P < 0.001$) women: RR = 0.75$P < 0.0002$)	Adjusted for age and comorbidity. Similar findings seen when excluding first 3 years of follow-up.
Villeneuve et al., 1998, Canada (49)	Prospective cohort (Canada Fitness Survey), 6246 men and 8196 women aged 20–69 yr	7 yr; 1116	Average daily energy expenditure (KKD = kcal·kg^{-1} body weight·d^{-1}) on LTPA estimated from modified Minnesota LTPA questionnaire	vs lowest KKD (<0.5), men 0.5 to <1.5 KKD: RR = 0.81 (0.59–1.11) 1.5 to <3.0 KKD: RR = 0.79 (0.54–1.13) ≥3.0 KKD: RR = 0.86 (0.61–1.22) vs lowest KKD (<0.5), women 0.5 to <1.5 KKD: RR = 0.94 (0.69–1.30) 1.5 to <3.0 KKD: RR = 0.92 (0.64–1.34) ≥3.0 KKD: RR = 0.71 (0.45–1.11) Among subjects without vigorous (<6 METs) LTPA, vs lowest KKD (<0.5) in nonvigorous LTPA, men 0.5 to <1.5 KKD: RR = 0.81 (0.59–1.17) 1.5 to <3.0 KKD: RR = 0.70 (0.44–1.13) ≥3.0 KKD: RR = 0.82 (0.53–1.27) Among subjects without vigorous (<6 METs) LTPA, vs lowest KKD (<0.5) in nonvigorous LTPA, women 0.5 to <1.5 KKD: RR = 0.97 (0.69–1.36) 1.5 to <3.0 KKD: RR = 0.87 (0.57–1.33) ≥3.0 KKD: RR = 0.72 (0.43–1.21) Participation in vigorous (≥6 METs) LTPA men: RR = 0.72 (0.53–0.96) women: RR = 0.71 (0.48–1.05)	Adjusted for age and smoking
			3 levels of fitness based on Canadian Aerobic Fitness Test	vs recommended fitness level minimum: RR = 1.02 (0.69–1.51) undesirable: RR = 1.52 (0.72–3.18)	
Weller and Corey 1998, Canada (51)	Prospective cohort (Canada Fitness Survey), 6620 women aged ≥30 yr	7 yr; 449	Average daily energy expenditure (KKD = kcal·kg^{-1} body weight·d^{-1}) on all activities estimated from modified Minnesota LTPA questionnaire	vs lowest KKD quartile (Q1) of leisure activity Q2: RR = 0.91 (0.66–1.25) Q3: RR = 0.94 (0.72–1.23) Q4: RR = 0.89 (0.67–1.17) vs lowest KKD quartile (Q1) of nonleisure activity Q2: RR = 0.66 (0.50–0.87) Q3: RR = 0.68 (0.51–0.89) Q4: RR = 0.71 (0.50–0.87)	Adjusted for age.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Wannamethee et al., 1998, UK (50)	Prospective cohort (British Regional Heart Study), 7735 men aged 40–59 yr free of CVD and diabetes	15 yr; 1064	6 categories of physical activity based on physical activity score derived from intensity and frequency of activities reported on questionnaire	vs inactive Occasional: RR = 0.79 (0.64–0.96) Light: RR = 0.69 (0.56–0.86) Moderate: RR = 0.64 (0.50–0.81) Moderately vigorous: RR = 0.63 (0.48–0.82) Vigorous: RR = 0.54 (0.38–0.77)	Adjusted for age, smoking, alcohol use, and BMI.
Kushi et al., 1997, USA (18)	Prospective cohort (Iowa Women's Health Study), 40,417 women aged 55–69 yr	7 yr; 2260	Frequency of moderate and vigorous LTPA assessed by questionnaire	vs rarely/never participating in moderate activity 1/wk–few/mo: RR = 0.71 (0.63–0.79) 2–4 times/wk: RR = 0.63 (0.56–0.71) >4 times/wk: RR = 0.59 (0.51–0.67) *P* for trend, <0.001 vs rarely/never participating in vigorous activity 1/wk–few/mo: RR = 0.83 (0.69–0.99) 2–4 times/wk: RR = 0.74 (0.59–.093) >4 times/wk: 0.62 (0.42–0.90) *P* for trend, 0.009	Adjusted for age; reproductive factors; alcohol use; total energy intake; smoking; estrogen use; BMI at baseline and 18 yr; waist-to-hip ratio; high blood pressure; diabetes; education level; marital status; and family history of cancer. Similar findings observed when excluding women with CVD or cancer and first 3 yr of follow-up.
			3-level LTPA index based on frequency and intensity of activity	low activity index Medium: RR = 0.77 (0.69–0.86) High: RR = 0.68 (0.60–0.77) *P* for trend, <0.001	
Morgan and Clarke, 1997, UK (31)	Prospective cohort (Nottingham longitudinal study of aging and activity), 406 men and 635 women aged ≥65 yrs	10 yr; 568	3 levels of physical activity assessed by interview using detailed inventory of activities	vs high activity, men Intermediate: RR = 1.35 (0.96–1.89) Low: RR = 1.59 (1.12–2.25) vs high activity, women Intermediate: RR = 1.53 (1.12–2.09) Low: RR = 2.07 (1.53–2.79)	Adjusted for age, health index score, and smoking.
Rosengren and Wilhelmsen, 1997, Sweden (40)	Prospective cohort (Göteborg study), 7142 men aged 47–55 yr at baseline	20 yr; 684	4 levels of LTPA and OPA assessed by questionnaire. Few men fell into the highest level of LTPA so top 3 levels combined	vs sedentary LTPA Moderately active: RR = 0.84 (0.77–0.93) Regular exercise: RR = 0.83 (0.77–0.90) No significant association with OPA.	Adjusted for age, diastolic blood pressure, serum cholesterol, smoking, alcohol use, BMI, diabetes, and occupation.
Haapanen et al., 1996, Finland (12)	Prospective cohort, 1072 men aged 35–63 yr	10.8 yr; 168	Energy expenditure index assessed by questionnaire asking 23 questions on LTPA, household chores, and commuting	vs >2100 kcal·wk^{-1} 1500.1–2100 kcal·wk^{-1}: RR = 1.74 (0.87–3.50) 800.1–1500 kcal·wk^{-1}: RR = 1.10 (0.55–2.21) <800 kcal·wk^{-1}: RR = 2.74 (1.46–5.14) *P* for trend, <0.0001 Specific activities showing independent inverse associations were leisure time forestry work, gardening, and repair work	Adjusted for age. Men who were unable to participate in physical activity because of ill health were excluded.
Kampert et al., 1996, USA (14)	Prospective cohort (Aerobics Center Longitudinal Study), 25,341 men and 7080 women aged 20–88 yr	8 yr; 690	Physical fitness determined by maximal exercise test on treadmill	vs lowest fitness quintile (Q1), men Q2: RR = 0.55 (0.44–0.70) Q3: RR = 0.61 (0.48–0.78) Q4: RR = 0.52 (0.41–0.66) Q5: RR = 0.49 (0.37–0.64) *P* for trend, <0.001 vs lowest fitness quintile (Q1), women Q2: RR = 0.53 (0.30–0.95) Q3: RR = 0.56 (0.31–1.01) Q4: RR = 0.22 (0.10–0.49) Q5: RR = 0.37 (0.19–0.72) *P* for trend, <0.001	Adjusted for age, examination year, smoking, chronic illness, and ECG abnormalties.
Kaplan et al., 1996, USA (16)	Prospective cohort (Alameda County Study), 2832 men and 3299 women aged 16–94 yr	28 yr; 1226	LTPA index assessed using answers to three questions on physical exercise, sports participation, and swimming	vs lowest LTPA tertile (T1), men T2: RR = 0.46 T3: RR = 0.31 vs lowest LTPA tertile (T1), women T2: RR = 0.42 T3: RR = 0.22	Unadjusted. Adjustment for age, sex, ethnicity, education, health conditions, and social isolation still yielded significant inverse associations.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
LaCroix et al., 1996, USA (19)	Prospective cohort study, 615 men and 1030 women aged ≥65 without severe disability or CHD	4.2 yr; 128	Modified Minnesota LTPA	vs walked <1 h·wk^{-1} 1–4 h·wk^{-1}: RR = 0.83 (0.53–1.29) >4 h·wk^{-1}: RR = 0.91 (0.58–1.42)	Adjusted for age, sex, functional status, smoking, BMI, chronic disease score, self-rated health, and alcohol use. Inverse association significant for women but not men, and for ≥75 yr but not 65–74 yr.
Lissner et al., 1996, Sweden (27)	Prospective cohort (Gothenborg Prospective Study of Women), 1405 healthy women aged 38–60 yr free of CVD, cancer, and diabetes	20 yr; 424	LTPA and OPA in the 12 months before baseline assessed from questionnaire in 1968–69 and 1974–75	vs low OPA in 1968–69 Medium: RR = 0.28 (0.17–0.46) High: RR = 0.24 (0.14–0.43) vs low LTPA in 1968–69 Medium: RR = 0.56 (0.39–0.82) High: RR = 0.45 (0.24–0.86) Women who increased their LTPA between 1968–69 and 1974–75, compared with no change: RR = 1.11 (0.67–1.86); those who decreased LTPA, compared with no change, RR = 2.07 (1.39–3.09)	Adjusted for age. Findings little changed with additional adjustment for smoking, alcohol use, education, BMI, waist-to-hip ratio, diet, blood pressure, blood lipids, and peak expiratory flow.
Mensink et al., 1996, Germany (30)	Prospective cohort (German Cardiovascular Prevention Study), 7689 men and 7747 women aged 25–69 yr	5–8 yr; 110	Questionnaire assessed 18 leisure activities; one question on OPA. Total activity, LTPA, conditioning activities (all except walking, cycling, gardening) and sports examined separately	vs low total activity, men Moderate: RR = 0.56 (0.30–1.04) High: RR = 0.78 (0.42–1.44) vs low LTPA, men Moderate: RR = 0.61 (0.35–1.05) High: RR = 0.79 (0.48–1.31) vs low conditioning activity, men Moderate: RR = 0.76 (0.44–1.34) High: RR = 0.67 (0.36–1.25) vs no sports activity, men <1 h·wk^{-1}: RR = 0.49 (0.26–0.95) 1–2 h·wk^{-1}: RR = 0.57 (0.30–1.09) >2 h·wk^{-1}: RR = 0.36 (0.16–0.79) vs low total activity, women Moderate: RR = 1.24 (0.60–2.58) High: RR = 1.29 (0.58–2.85) vs low LTPA, women: Moderate: RR = 0.94 (0.51–1.75) High: RR = 0.81 (0.44–1.49) vs low conditioning activity, women: Moderate: RR = 0.38 (0.13–1.06) High: RR = 0.80 (0.42–1.54) vs no sports activity, women: <1 h·wk^{-1}: RR = 0.38 (0.12–1.23) 1–2 h·wk^{-1}: RR = 0.52 (0.23–1.17) >2 h·wk^{-1}: RR = 0.28 (0.07–1.17)	Adjusted for age, systolic blood pressure, total serum cholesterol, BMI, and smoking.
Eaton et al., 1995, Israel (9)	Prospective cohort (Israeli Ischemic Heart Disease Study), 8463 men aged ≥40 yr free of CVD	21 yr; 2593	LTPA and OPA assessed by interview using 2 questions with 4 responses each	vs sedentary LTPA Light: RR = 0.84 (0.74–0.94) Light daily: RR = 0.81 (0.73–0.90) Heavy: RR = 0.84 (0.72–0.98) vs sitting OPA Standing: RR = 0.99 (0.88–1.12) Walking: RR = 1.09 (0.99–1.20) Physical labor: RR = 1.16 (1.03–1.30)	Adjusted for age.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Lee et al., 1995, USA (21)	Prospective cohort (Harvard Alumni Health Study), 17,321 men, mean age 46 yr free of CVD, COPD, and cancer	22–26 yr; 3728	Nonvigorous (<6 METs) and vigorous (≥6 METs) LTPA energy expenditure derived from questionnaire asking about walking, stair climbing, and sports/recreation	vs lowest nonvigorous activity (energy expenditure <630 kJ·wk^{-1}) 630–1679 kJ·wk^{-1}: RR = 0.89 (0.79–1.01) 1680–3149 kJ·wk^{-1}: RR = 1.00 (0.89–1.12) 3150–6299 kJ·wk^{-1}: RR = 0.98 (0.88–1.12) ≥6300 kJ·wk^{-1}: RR = 0.92 (0.82–1.02) *P* for trend, 0.36 vs lowest vigorous activity (energy expenditure <630 kJ·wk^{-1} 630–1679 kJ·wk^{-1}: RR = 0.88 (0.82–0.96) 1680–3149 kJ·wk^{-1}: RR = 0.92 (0.82–1.02) 3150–6299 kJ·wk^{-1}: RR = 0.87 (0.77–0.99) ≥6300 kJ·wk^{-1}: RR = 0.87 (0.78–0.97) *P* for trend, 0.007	Adjusted for age, BMI, smoking, hypertension, diabetes, and early parental death; mutually adjusted for the 2 kinds of energy expenditure.
Sherman et al., 1994, USA (42)	Prospective cohort (Framingham Heart Study), 1404 women aged 50–74 yr free of CVD	16 yr; 319	Time spent sleeping, resting, or engaged in light, moderate, or heavy physical activity assessed by interview	vs lowest activity quartile (Q1) Q2: RR = 0.93 (0.70–1.23) Q3: RR = 0.65 (0.47–0.90) Q4: RR = 0.68 (0.49–0.94)	Adjusted for age, systolic blood pressure, serum cholesterol, smoking, weight, and presence or absence of glucose intolerance, LVH, COPD, and cancer. Excluding first 6 years of follow-up yielded similar results.
Sherman et al., 1994, USA (43)	Prospective cohort (Framingham Heart Study), 96 men and 189 women aged ≥75 yr free of CVD	10 yr; (N/A)	Time spent sleeping, resting, or engaged in light, moderate, or heavy physical activity assessed by interview	vs lowest activity quartile (Q1), men Q1: RR = 0.67 (0.32–1.38) Q3: RR = 0.59 (0.26–1.34) Q4: RR = 0.46 (0.20–1.03) vs lowest activity quartile (Q1), women Q2: RR = 0.70 (0.38–1.29) Q3: RR = 0.26 (0.12–0.55) Q4: RR = 0.39 (0.20–0.77)	Adjusted for age, systolic blood pressure, serum cholesterol, smoking, weight, and presence or absence of glucose intolerance, LVH, COPD, and cancer. Excluding first 3 years of follow-up yielded similar results.
Blair et al., 1993, USA (4)	Prospective cohort (Aerobics Center Longitudinal Study), 10,224 men, mean age 41.7 yr, and 3120 women, mean age 40.9 yr	8 yr; 283	LTPA assessed by questionnaire asking about 18 common activities. Subjects with no activities were classified as inactive, those who walked, jogged, or ran as highly active, and all others as moderately active	vs high LTPA, men Moderate: RR = 1.48 (0.9–2.42) Low: RR = 1.70 (1.06–2.74) *P* for trend, <0.001 vs high LTPA, women Moderate: RR = 0.75 (0.41–1.39) Low: RR = 0.95 (0.54–1.70) *P* for trend, 0.31	Adjusted for age.
Paffenbarger et al., 1993, USA (35)	Prospective cohort (Harvard Alumni Study), 10,269 men aged 45–84 yr	9 yr; 476	LTPA index (kcal·wk^{-1}) derived from questionnaires in 1962 or 1966 and 1977 asking about walking, climbing stairs, and participating in sports/recreation	vs <500 kcal·wk^{-1} in 1977 500–999 kcal·wk^{-1}: RR = 0.73 (0.54–0.95) 1000–1499 kcal·wk^{-1}: RR = 0.71 (0.53–0.96) 1500–1999 kcal·wk^{-1}: RR = 0.64 (0.46–0.92) 2000–2499 kcal·wk^{-1}: RR = 0.57 (0.40–0.87) 2500–2999 kcal·wk^{-1}: RR = 0.74 (0.50–1.12) 3000–3499 kcal·wk^{-1}: RR = 0.81 (0.52–1.32) ≤3500 kcal·wk^{-1}: RR = 0.52 (0.39–0.75) *P* for trend, <0.001	Adjusted for age.
				Taking up activities of ≥4.5 METs between 1962/1966 and 1977, compared with not engaging in these activities at both times RR = 0.77 (0.58–0.96)	Adjusted for age, smoking, BMI, hypertension, and total energy expenditure.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Sandvik et al., 1993, Norway (41)	Prospective cohort, 1960 healthy men aged 40–59 yr	16 yr; 271	Physical fitness determined by maximal exercise test on bicycle ergometer	vs lowest fitness quartile (Q1) Q2: RR = 0.59 (0.28–1.22) Q3: RR = 0.45 (0.22–0.92) Q4: RR = 0.41 (0.20–0.84)	Adjusted for age, smoking, systolic blood pressure, lipids, vital capacity, glucose tolerance, resting heart rate, BMI, and physical activity level. Physical activity unrelated to mortality after accounting for physical fitness.
Simonsick et al., 1993, USA (44)	3 prospective cohorts (Established Populations for Epidemiologic Studies of the Elderly), 2264 men and 2913 women aged ≤65 yr	6 yr; (N/A)	LTPA assessed by interview; different questions used at different sites. In all sites, "highly active" persons participated in vigorous exercise or active sports	vs inactive, East Boston Moderately active: RR = 0.85 (0.63–1.15) Highly active: RR = 0.73 (0.48–1.11) vs inactive, New Haven Moderately active: RR = 0.81 (0.60–1.11) Highly active: RR = 0.66 (0.45–0.95) vs inactive, Iowa Moderately active: RR = 1.06 (0.77–1.46) Highly active: RR = 0.59 (0.37–0.92)	Adjusted for age, sex, education, work status, smoking, respiratory symptoms, MI, stroke, diabetes, angina, self-rated health, and modified depression score.
Weyerer, 1993, Germany (52)	Prospective cohort, 1536 men and women aged ≥15 yr	5 yr; 79	LTPA assessed by interview with the question, "How often do you currently exercise for sports (never, occasionally, or regularly)?"	vs regular LTPA, men Occasional: RR = 1.50 (0.46–4.89) Never: RR = 1.76 (0.65–4.75) vs regular LTPA, women Occasional: RR = 1.14 (0.24–5.30) Never: RR = 1.51 (0.41–5.54)	Adjusted for age, social class, physical and psychiatric disorders.
Rakowski and Mor, 1992, USA (38)	Prospective cohort (Longitudinal Study of Aging), 2222 men and 3679 women aged ≥70 yr	4 yr; 1098	LTPA assessed by responses to questions: "How often do you walk a mile or more at a time?" and "Compared with other persons your age, would you say you are physically more active, less active, or the same?"	vs walk 4+ d·wk^{-1}, men 2–3 d·wk^{-1}: RR = 1.15 (0.70–1.90) 1 d·wk^{-1}: RR = 1.20 (0.74–1.94) <1 d/never: RR = 1.23 (0.93–1.62) vs walk 4+ d·wk^{-1}, women 2–3 d·wk^{-1}: RR = 1.72 (1.01–2.05) 1 d·wk^{-1}: RR = 1.48 (0.70–3.10) <1 d/never: RR = 2.49 (1.64–3.80) vs more/much more activity than peers, men Same: RR = 1.29 (0.99–1.67) Less/much less: RR = 1.77 (1.16–2.70) vs more/much more activity than peers, women Same: RR = 1.31 (1.05–1.63) Less/much less: RR = 1.48 (1.05–2.09)	Adjusted for age, sex, race, education, living arrangement, self-rated health, social involvement, heart condition, hypertension, stroke, diabetes, functional status, and BMI.
Leon et al., 1991, USA (24)	Prospective cohort (Multiple Risk Factor Intervention Trial [MRFIT]), 12,138 men aged 35–57 yr at high risk for CHD	10.5 yr; 958	LTPA assessed by Minnesota LTPA questionnaire	vs lowest tertile of LTPA (T1) T2: RR = 0.89 (0.77–1.04) T3: RR = 0.92 (0.79–1.07)	Adjusted for age, treatment group assignment, baseline serum cholesterol, diastolic blood pressure, and smoking.
Lindsted et al., 1991, USA (26)	Prospective cohort (Adventist Mortality Study), 9484 men aged ≥30 yr	26 yr; 4000	Total LTPA and OPA assessed by the question, "How much exercise do you get (work or play)?"	vs low total activity, attained age 50 Moderate: RR = 0.61 (0.50–0.74) High: RR = 0.66 (0.50–0.87) vs low total activity, attained age 60 Moderate: RR = 0.68 (0.59–0.78) High: RR = 0.76 (0.63–0.92) vs low total activity, attained age 70 Moderate: RR = 0.76 (0.69–0.83) High: RR = 0.89 (0.78–1.01) vs low total activity, attained age 80 Moderate: RR = 0.85 (0.78–0.92) High: RR = 1.03 (0.91–1.16) vs low total activity, attained age 90 Moderate: RR = 0.94 (0.84–1.06) High: RR = 1.19 (0.99–1.43)	Adjusted for race, smoking, education, medical illness, BMI, marital status, and diet.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Lee and Markides, 1990, USA (20)	Prospective cohort, 508 men and women aged ≥60 yr	8 yr; 119	LTPA scale derived from answers to 10-item questionnaire	No significant trend for increasing LTPA, $P > 0.05$	Adjusted for age, sex, ethnicity, education, and self-rated health.
Blair et al., 1989, USA (6)	Prospective cohort (Aerobics Center Longitudinal Study), 10,224 men, mean age 41.7 yr, and 3120 women, mean age 40.9 yr	8 yr; 283	Physical fitness determined by maximal treadmill exercise test	vs highest fitness quintile (Q5), men Q4: RR = 1.17 (0.63–2.17) Q3: RR = 1.46 (0.81–2.63) Q2: RR = 1.37 (0.76–2.50) Q1: RR = 3.44 (2.05–5.77) *P* for trend, <0.05 vs highest fitness quintile (Q5), women Q4: RR = 0.76 (0.27–2.11) Q3: RR = 1.43 (0.60–3.44) Q2: RR = 2.42 (1.09–5.37) Q1: RR = 4.65 (2.22–9.75) *P* for trend, <0.05	Adjusted for age.
Slattery et al., 1989, USA (46)	Prospective cohort (U.S. Railroad Study), 3043 middle-aged men free of CVD	17–20 yr; (N/A)	Weekly energy expended in LTPA, derived from Minnesota LTPA questionnaire	vs >2000 kcal·wk^{-1} 1001–1999 kcal·wk^{-1}: RR = 1.04 (1.01–1.08) 251–1000 kcal·wk^{-1}: RR = 1.08 (1.01–1.15) ≤250 kcal·wk^{-1}: RR = 1.21 (1.03–1.42)	Adjusted for age, systolic blood pressure, serum cholesterol level, and smoking. In simultaneous analyses of light/moderate and vigorous activities, only vigorous activity was significantly and inversely related to all-cause mortality.
Slattery and Jacobs, 1988, USA (45)	Prospective cohort (US Railroad Study), 2431 men aged 22–79 yr free of CVD	17–20 yr; 630	Physical fitness assessed by heart rate on submaximal 3-minute treadmill test	vs ≤105 beats·min^{-1} 106–115 beats·min^{-1}: RR = 1.07 (1.02–1.13) 116–127 beats·min^{-1}: RR = 1.15 (1.10–1.21) ≥127 beats·min^{-1}: RR = 1.23 (1.17–1.30)	Adjusted for age, systolic blood pressure, serum cholesterol, and smoking. Similar associations seen among men with <1000 kcal·wk^{-1} or ≥1000 kcal·wk^{-1} in LTPA.
Leon et al., 1987, USA (25)	Prospective cohort (Multiple Risk Factor Intervention Trial [MRFIT]), 12,138 men aged 35–57 yr at high risk of CHD	7 yr; 488	LTPA assessed by Minnesota LTPA questionnaire	vs lowest tertile (T1) T2: RR = 0.73 (0.59–0.91) T3: RR = 0.87 (0.70–1.07)	Adjusted for age, diastolic blood pressure, serum cholesterol, smoking, and treatment group.
Paffenbarger, et al., 1986, USA (34)	Prospective cohort (Harvard Alumni Study), 16,936 men aged 35–74 yr and free of CHD	12–16 yr; 1413	LTPA index (kcal·wk^{-1}) derived from questionnaire asking about walking, climbing stairs, and participating in sports/ recreation	vs <500 kcal·wk^{-1} 500–999 kcal·wk^{-1}: RR = 1.00 1000–1499 kcal·wk^{-1}: RR = 0.73 1500–1999 kcal·wk^{-1}: RR = 0.63 2000–2499 kcal·wk^{-1}: RR = 0.62 2500–2999 kcal·wk^{-1}: RR = 0.52 3000–3499 kcal·wk^{-1}: RR = 0.46 ≤3500 kcal·wk^{-1}: RR = 0.62 *P* for trend, <0.0001	Adjusted for age.
Menotti and Seccareccia, 1985, Italy (29)	Prospective cohort (Italian Railroad Study), 99,049 men aged 40–59 yr	5 yr; 2661	OPA based on estimated energy cost of task performed	vs. sedentary OPA Moderate: RR = 1.03 ($P > 0.05$) Heavy: RR = 1.04 ($P > 0.05$)	
Kannel and Sorlie, 1979, USA (15)	Prospective cohort (Framingham Heart Study), 1909 men and 2311 women aged 35–69	14 yr; 552	Physical activity index derived from interview on hours resting and various job and extracurricular activities	No significant trend for increasing physical activity index in men and women, $P > 0.05$	Adjusted for age, systolic blood pressure, smoking, serum cholesterol, glucose intolerance, and LVH. Physical activity significantly associated with lower CHD rates in men.

TABLE 1. *Continued*

Author, Year, Country	Study Design and Population	Duration of Follow-up; Number of Deaths	Definition of Physical Activity	Main Results*	Comments
Breslow and Buell, 1960, USA (7)	Proportional mortality study, 2,984,867 male California workers aged 20–64	(not applicable); 72,664	OPA derived from Census Bureau occupational list	vs sedentary OPA Light: RR = 1.10 Medium: RR = 1.21 Heavy nonfarm: RR = 1.52 Heavy farm: RR = 1.11	Data from death certificates. Did not adjust for smoking. CHD mortality lower among workers with heavy OPA.
Morris and Heady, 1953, UK (32)	Mortality study, ≈2.5 million male British workers aged 45–64	(not applicable); 5,037	OPA estimated from job descriptions	vs light OPA, smoking possible occupations Intermediate/doubtful: RR = 1.00 Heavy: RR = 0.75 vs light OPA, smoking prohibited occupations Intermediate/doubtful: RR = 0.52 Heavy: RR = 0.37	Data from death certificates. Smoking prohibited occupations included miners, textile workers, those in chemical processes, policemen, and printers.

* Figures in parentheses are 95% confidence limits. If not provided, they were not available. *P*-values for trend come from tests of linear trend.
BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; LTPA, leisure time physical activity; LVH, left ventricular hypertrophy; MET, metabolic equivalent; MI, myocardial infarction; N/A, not available; OPA, occupational physical activity; RR, relative risk.

both of which will generate a volume of energy expenditure on the order of 1000 kcal·wk^{-1}, is likely to decrease all-cause mortality rates. However, we cannot rule out that a lesser volume of physical activity may be associated with benefit for all-cause mortality (18,25,35).

Intensity of physical activity. To ascertain the dose response between intensity of physical activity and all-cause mortality, activities of different intensity must be simultaneously considered to prevent confounding by volume of physical activity. As discussed earlier, a larger volume of physical activity is clearly associated with decreased all-cause mortality rates, and vigorous-intensity activities generate higher levels of energy expenditure than moderate-intensity activities when time is held constant. Alternately, investigators can examine select populations that engage only (or primarily) in moderate-intensity or vigorous-intensity activity. Although such studies can answer the question of whether moderate-intensity or vigorous-intensity physical activity is associated with decreased all-cause mortality rates, they do not allow direct comparison of the merits of moderate-intensity activity with vigorous-intensity activity; i.e., dose-response with intensity.

Only four studies examined intensity of physical activity, simultaneously considering physical activity of other intensities; one reported that moderately vigorous (≥4.5 METs) activities were beneficial compared with activities of lesser intensity (35), whereas three noted that only vigorous physical activity (≥6 METs), but not less-intense physical activity, predicted lower all-cause mortality rates (21,22,46).

Some of the studies examined intensity of physical activity in relation to all-cause mortality rates but did not simultaneously adjust for activities of different intensities. Among Danish subjects with any LTPA, participation in sports conferred further risk reduction for all-cause mortality (2). Participation in vigorous activities of ≥ 6 METs was associated with a lower risk of all-cause mortality in Finnish subjects (17). In German subjects, participation in sports but not other activities reduced rates of all-cause mortality (30). In all three of these studies, it is unclear whether the findings reflect additional benefit with greater volume of physical activity from participation in sports or vigorous activities. In three other studies where subjects engaged primarily in moderate-intensity physical activity, investigators did observe a benefit for all-cause mortality with increasing levels of participation in these activities (13,18,25).

Duration and frequency of physical activity. To isolate the effect of duration or frequency of physical activity on all-cause mortality rates, it is imperative to hold volume of physical activity constant to prevent confounding by volume of activity. In other words, if two individuals expend the same volume of energy, does it matter whether one expends this volume in several, shorter bouts of physical activity or in fewer, longer bouts?

None of the 44 studies addressed this question in relation to all-cause mortality. One recent study did examine this issue in relation to coronary heart disease (CHD) (23). The investigators concluded that duration (examined in 15-min intervals) and frequency did not predict CHD rates once volume of physical activity was accounted for. That is,

shorter sessions of exercise had similar effects on CHD risk compared with longer sessions, as long as the total energy expended was similar.

Four of the studies in Table 1 examined duration (19) or frequency (18,30,38) of physical activity in relation to all-cause mortality rates. However, because the analyses did not control for volume of physical activity, the findings essentially reflect the association between volume of physical activity and all-cause mortality.

DISCUSSION

There is a sufficient body of evidence to evaluate the dose-response relation between physical activity and all-cause mortality rates. We identified 44 studies conducted in Canada, Denmark, Finland, Germany, Israel, Italy, the Netherlands, Norway, Sweden, the United Kingdom, and United States that addressed this issue. Based on these studies, there is clear evidence of an inverse dose-response relation between volume of physical activity (or level of physical fitness) and all-cause mortality rates. The preponderance of evidence suggests that risk of dying during a given period continues to decline with increasing levels of physical activity rather than displaying a threshold or L-shaped relation. This inverse dose-response relation has been shown in men and women, and in younger and older ($\geq$60 yr) subjects.

Fewer data are available regarding the volume of physical activity needed to reduce all-cause mortality rates. It appears that minimal adherence to current or previous physical activity recommendations, which will generate energy expenditure on the order of 1000 kcal·wk^{-1}, results in decreased all-cause mortality rates with risk reductions on the order of 20–30%. In addition, three studies suggest that an even lower volume of physical activity may be associated with benefit (18,25,35).

Sparse data exist regarding the components that contribute to the volume of physical activity: intensity, duration, and frequency. Studies conducted in populations engaged primarily in moderate-intensity physical activity show that higher levels of moderate-intensity physical activity are associated with lower all-cause mortality rates, presumably because of higher volume of physical activity. However, hardly any data are available to determine for two individuals expending the same volume of physical activity whether there is additional benefit for the one who expends all of it in vigorous-intensity physical activity compared with the other who expends all of it in moderate-intensity activity.

No data are available to answer the questions on duration and frequency. That is, it is unknown whether a given volume of physical activity expended in shorter, more frequent bouts has different effects on all-cause mortality rates than that same volume expended in longer, less frequent bouts.

Although not directly relevant to the issue of dose response, an important public health issue is determining whether changing from a sedentary lifestyle to an active one (or from an unfit cardiorespiratory profile to a fit one) is associated with lower all-cause mortality rates. The studies reviewed suggest that increasing physical activity or fitness is associated with benefit (3,10,35), whereas decreasing levels is associated with harm (27). Two other studies that did not satisfy the criteria for this review also support the benefit of increasing physical activity or fitness levels (5,36).

Evidence category. All studies investigating dose-response associations between physical activity and all-cause mortality have been observational studies. No randomized clinical trial data are available. Therefore, the above conclusions are based on Evidence Category C.

Because the conclusions are based on observational studies, two potential limitations need to be considered. First, are the observed associations the result of bias? If poor health caused subjects to decrease their physical activity level before the start of the study, this would cause investigators to observe a spurious inverse relation between higher levels of physical activity and lower all-cause mortality rates. Such a bias is unlikely to account for the results because the inverse associations have been noted in studies that included only healthy subjects. It is also possible that apparently healthy subjects with undiagnosed, serious illnesses (who are likely to die in the early years of follow-up) may have decreased their physical activity before study entry. Employing a built-in lag period minimizes this bias. Several studies that considered a lag period observed an inverse association between physical activity and all-cause mortality rates. Finally, the effect of this bias is diluted with longer follow-up periods; many of the studies that reported an inverse association had periods of follow-up lasting 10 or more yr.

A second potential limitation is confounding by other health habits. Individuals who are physically active are likely to be health conscious in other ways as well, such as not smoking, eating a healthier diet, and maintaining a healthy weight. However, the inverse association between physical activity level and all-cause mortality rates are unlikely to be due to these other health habits, because studies that controlled for these potential confounders continued to observe an inverse association.

RESEARCH RECOMMENDATIONS

Although the most rigorous data for a cause-and-effect relation come from well-designed and conducted randomized clinical trials, it is simply not feasible to conduct such trials in the context of examining the dose-response relation between physical activity and all-cause mortality. Thus, answers concerning this relation must come from observational epidemiologic studies. These observational data will be strengthened by data from randomized clinical trials of physical activity and short-term health outcomes that in themselves predict mortality (e.g., blood pressure, lipid profile, glucose tolerance), as well as by data from laboratory studies on plausible biologic mechanisms linking physical activity with decreased mortality rates.

With regard to observational epidemiologic studies that directly assess the dose-response relation between physical

activity and all-cause mortality rates, we propose the following areas for future research:

1. Studies must assess physical activity in sufficient detail to permit translation of findings to public health recommendations. For example, studies asking subjects whether they get none, some, or a lot of physical activity during work or leisure-time are difficult to interpret with respect to the dose of physical activity. Assessment of the kinds of activity, the intensity (both on an absolute scale and relative to the capacity of the individual subject, the latter being especially relevant for older persons), duration, and frequency are desirable.

2. The existing data suggest that current and previous physical activity recommendations will generate sufficient volume of physical activity to decrease all-cause mortality rates. However, there are some provocative, but not definitive, data suggesting that an even lower volume of physical activity—perhaps half of what is currently recommended—may be all that is needed. This is important to ascertain because recommending an even lower volume of physical activity for health surely will be more palatable to the many sedentary individuals in the world.

3. It is unclear whether there is a dose-response relation between intensity of physical activity and all-cause mortality rates above the contribution of intensity to volume of physical activity. Future studies should analyze data on intensity of physical activity while controlling for volume of physical activity. Although expending the minimum volume of energy for health, whether from moderate- or vigorous-intensity physical activity, may be all that is relevant to the public, recommendations for higher-intensity activity may be more attractive to busy individuals because they deliver greater volume of activity in shorter time periods. They may be even more attractive if they engender additional benefit for all-cause mortality.

4. There are no data on whether duration and frequency of physical activity are important to all-cause mortality beyond their contribution to volume of physical activity. This area has direct bearing on the current physical activity recommendation that allows for accumulation of short bouts of physical activity. Future studies should analyze the associations of duration and frequency with all-cause mortality rate, controlling for the volume of energy expended.

5. There are no data on whether patterns of physical activity conforming to previous physical activity recommendations ("structured exercise") offer commensurate benefit for all-cause mortality rates as patterns of physical activity conforming to current physical activity guidelines ("lifestyle physical activity"), when the same volume of physical activity is generated. Studies that satisfy research recommendation (1) should have adequate information to classify subjects according to both patterns of physical activity and be capable of examining mortality rates in both groups.

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Physical activity and cardiovascular disease: evidence for a dose response

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ABSTRACT

KOHL, H. W., III. Physical activity and cardiovascular disease: evidence for a dose response. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S472–S483. **Purpose:** To summarize and synthesize existing literature providing evidence of a dose-response relation between physical activity and cardiovascular disease endpoints. **Methods:** MEDLINE search of indexed English-language literature through August 2000. Findings supplemented by existing consensus documents and other published literature. Only studies with greater than two physical activity exposure categories were included, and studies not focusing on the clinical manifestation of the outcome (incidence or mortality) were excluded. **Results:** Existing studies were classified by outcome used: all cardiovascular disease (CVD), coronary (ischemic) heart disease (CHD), and stroke. The vast majority of the literature in this area has relied on prospective observational studies and has been conducted in European men or populations of men of primarily European descent. Follow-up intervals ranged from 3 to 26 yr, and most studies related a single initial measure of physical activity to the outcome of interest, sometimes many years in the future. No randomized trials of physical activity and cardiovascular disease as a clinical outcome exist. Taken together, the available evidence indicates that cardiovascular disease incidence and mortality, and specifically ischemic heart disease, are causally related to physical activity in an inverse, dose-response fashion. These findings have been demonstrated in a variety of populations and using a variety of physical activity assessment methods. Contrarily, equivocal evidence for stroke incidence and mortality prohibits a similar conclusion. No strong evidence for dose-response relation between physical activity and stroke as a CVD outcome is available. **Conclusion:** Physical inactivity is prominent in the causal constellation for factors predisposing to cardiovascular disease, particularly ischemic heart disease. Methodologic advances in physical activity assessment; additional studies on changes in the antecedent variable, physical activity, as it relates to the outcome; and more studies among women and ethnically diverse populations are needed to clarify these relations. **Key Words:** CORONARY HEART DISEASE, STROKE, CARDIOVASCULAR DISEASE , ISCHEMIC HEART DISEASE, DOSE RESPONSE

Since the seminal and visionary studies of London Civil Servants (32), nearly a half-century of research has led to the immutable conclusion that physical inactivity is a prominent part of the causality constellation that increases the risk of cardiovascular disease. The cumulative effect of this body of work has led leading health authorities around the world at the dawn of this new millennium to make physical activity promotion for cardiovascular health part of broad ranging health policy and goals (3,8,37,38,54). This situation is in sharp contrast to the prevailing health concerns at the start of the previous century when control of infectious diseases was paramount.

Coronary heart disease (CHD) and stroke (CVA) are two manifestations of cardiovascular disease (CVD) in which there have been a variety of investigations of the role of preventive and therapeutic role of physical activity. Each outcome has several plausible biologic mechanisms through which physical activity has been hypothesized to interrupt or delay the pathogenic onset or development. These physiologic and biologic relationships between physical activity and health outcomes have been reviewed extensively (54).

Although these advances have been spectacular, much remains to be learned. Early observational studies in this area focused on bivariate categorization of activity status (categorization of study participants as active/inactive; active jobs/inactive jobs; leisure activity/no leisure activity) as a method of comparison and contrast of outcomes of interest. Only more recently have questions arisen regarding the "shape" of the relationship between physical activity and cardiovascular health. This natural progression of inquiry requires an understanding of a continuum of exposure instead of bivariate categorization, and how that continuum is related to the outcome of interest. Further, important interactions and effect-modifications such as those associated with gender, age, and ethnic identity differences for these dose-response questions become much more prominent when thought is extended past the bivariate case.

The purpose of this paper is to review available evidence regarding a dose-response relation between physical activity and fatal and nonfatal cardiovascular disease. Outcomes included are fatal and nonfatal stroke (ischemic and hemorrhagic) and fatal and nonfatal coronary (ischemic) heart disease. This review is limited to published studies with documented clinical manifestation of disease as outcomes. Studies in which biologic,

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pathologic, or diagnostic indicators of cardiovascular disease have been used as outcomes (without clinical manifestation) are excluded from this review. Further, to evaluate the potential dose-response pattern, studies that relied solely on a bivariate categorization of "exposure" of physical activity have been excluded.

This paper is organized into three separate sections according to the type of cardiovascular disease outcome reported: all CVD combined, CHD, and CVA. Tabulations for each of the three outcomes focus on critical points of study design, results, and interpretation. Tables are presented in each section summarizing key observational research findings as to the type of population studied, a brief description of assessment of the antecedent variable (physical activity) used in the study, the main outcome under consideration, and the main findings of the analyses. Further, if a dose-response association was observed in the study, the outcome is indicated either positively or negatively. Finally, each table also provides a brief area for ancillary comments related to the study.

CURRENT STATUS OF KNOWLEDGE

Cardiovascular disease. A summary of major population-based studies of physical activity and/or fitness as they relate to risk of CVD is highlighted in Table 1. All studies investigated CVD mortality as an endpoint, whereas only one reported on CVD incidence (fatal or nonfatal disease).

Five major observational studies (eight publications) have evaluated the association between physical activity and the risk of CVD and allow evaluation of a possible dose-response relation (4,17,18,26,29,35,45,49). All were prospective in design, were in large populations, and had long-term follow-up periods (follow-up times ranged from 5 to 26 yr). Four publications included women and two focused exclusively on women (45,49). Four of the eight studies focused exclusively on fatal CVD, whereas the remainder included a mixture of fatal and nonfatal outcomes. Among the eight publications, two showed no evidence of a dose response relation between physical activity and CVD risk (26,49); one reported mixed results using various physical activity indices, and the remaining five were judged to demonstrate convincing evidence of a dose-response relation. Of note, the two most recent studies (4,45) observed dose-response relations, the former among older men and the latter among women. All studies relied on a single baseline point estimate of physical activity, in some cases assessed up to 26 yr before the end of the observational period.

Taken together, the major observational studies relating the risk of CVD incidence and mortality to physical activity indicate that the relation is likely causal, and the majority provide convincing evidence for a dose-response relation. A limitation of these studies, however, is that CVD is a large collection of diseases and disorders, many which may not be related to the atherosclerotic process or other biologic mechanisms that may be affected by physical activity. Further, the baseline assessment of physical activity as it relates to a CVD event in the distant future (up to 26 yr in the studies reviewed) does not take into account changes in behavior and clinical and physiologic status during the follow-up period. Thus, proximity of the exposure to the outcome becomes critical in these studies and points to the need for studies that assess changes in exposure, potential confounding variables, and outcome risk over time.

Coronary heart disease. Beginning with the seminal work by Morris et al. (32), nearly 50 yr of work have accumulated a vast literature on the role that physical activity may play in the risk of CHD. These studies have examined the issue in populations worldwide and have examined physical activity as it relates to both occupation and leisure pursuits. Thorough and methodologically rigorous reviews have been published on the association of physical activity with CHD (2,5,39, and others) and have concluded that physical inactivity is causally linked to an increased risk of CHD. A substantial subset of these studies allows evaluation of the possibility of a dose-response relation. A summary of these major studies relating risk of CHD to dose of physical activity is presented in Table 2.

Twenty-three major observational studies, represented by 31 publications relating dose of physical activity to risk of CHD have been published since 1958 (6,9,10,11,16,19,23–25,28,30,31,33,34,36,40–42,44,46–48,50–53,56). Studies published before 1978 relied almost exclusively on determination of physical activity exposure by creating occupational classifications based on physical demands of job tasks. Thereafter, physical activity pursuits during leisure-time formed the bases for antecedent variable definition for most studies. Moreover, most studies before 1978 were not able to statistically control for potentially confounding variables. Thus, point estimates of risk are based on age-adjusted incidence alone in these studies.

One of the 23 studies was a large case series (31), one was a case-comparison design (24), and one was a secondary analysis of a large randomized clinical trial on CHD (25), although the original purpose of the study was not a physical activity intervention. The remainder of the studies were prospective in design, were in large populations, and had long-term follow-up periods (follow-up times ranged from 3 to 26 yr). Four publications (all published since 1995) included women, and two focused exclusively on women (24,52).

Most studies focused on age ranges of participants associated with risk of CHD (30–88 yr), and 9 of the 23 studies focused exclusively on fatal CHD whereas the remainder included a mixture of fatal and nonfatal outcomes. All studies but one (56) relied on a single point estimate of physical activity at the baseline assessment and related that to risk of CHD during follow-up.

Twenty of the reviewed studies were judged to provide support for a dose-response relation between physical activity and CHD. An additional three studies (9,33,47) provided mixed support for such a relation depending on the indices of physical activity used or cohort characteristics (data stratification) presented. Eight studies did not support the conclusion of a dose-response relation between physical activity and CHD (16,40,42,44,51). Results in these varied from null associations (16,40,42,51) to suggestions of threshold (41,48) to a

TABLE 1. Population-based studies of association of physical activity as related to cardiovascular disease (CVD): English literature, 1953–August 2000.

Study	Population	Antecedent Variable	Definition of Cardiovascular Disease	Main Findings	Dose Response	Comments
Kannel and Sorlie (1979) (18)	1909 Framingham men and 2311 women aged 35–64 at fourth biennial examination; 14-yr follow-up.	Physical activity index based on hours per day spent at activity-specific intensity.	CVD mortality and incidence. Men: (N = 140 deaths, N = 435 incident cases). Women: (N = 101 deaths).	Inverse association between physical activity index and mortality. Not statistically significant for either men or women. Inverse (and significant) association between physical activity index and CVD incidence.	Yes. Based on duration and intensity.	Control for several confounding variables.
Paffenbarger et al. (1984) (35)	16,936 male college alumni who entered college between 1916 and 1950; followed from 1962–1978.	Physical activity index (kcal·wk^{-1}) estimated from reports of stairs climbed, city blocks walked and sports play each week.	Death due to CVD (N = 640).	Inverse association. Relative to highest category of index (2000+ kcal·wk^{-1}), risk estimates in next two lower categories were 1.28 and 1.84, respectively.	Yes. Based on intensity and frequency.	Significant dose-response trend after adjusting for differences in age, cigarette smoking and hypertension prevalence.
Kannel et al. (1986) (17)	1166 Framingham men aged 45–64 yr; 24 yr of follow-up.	Physical activity index based on hours per day at activity-specific intensity. Occupational physical activity classified by physical demand of work.	Death due to CVD (N = 325).	Inverse association. For physical activity index, age-adjusted RR (relative to high category) = 1.62 (low), 1.30 (moderate). For occupational activity, age-adjusted RR (relative to heavy category) = 1.34 (sedentary), 1.26 (light), 1.09 (medium).	Yes. Based on duration and intensity.	Inverse association constant across all analyses. Inverse association maintained after multivariate confounding control.
Lindsted et al. (1991) (26)	9484 Seventh-day Adventist men aged 30 yr and over; 26-yr follow-up.	Self-report to single physical activity question.	CVD (ICD-8 410-458) (N = 3799).	Null association. Risk estimates of CVD mortality for moderate and high activity groups, relative to low group were 0.79 (95% CI = 0.58–1.07) and 1.02 (95% CI = 0.66–1.58).	No. Based on single question of self-ascribed intensity.	Possible protective association among moderate activity group.
Sherman et al. (1994) (49)	1404 Framingham women aged 50–74 yr; 16 yr of follow-up.	Physical activity index based on hours per day spent at activity-specific intensity.	CVD incidence and mortality.	Null association across quartiles of physical activity index for CVD mortality and incidence.	No. Based on duration and intensity.	No statistical significance after controlling for several confounding variables.
Mensink et al. (1996) (29)	1061 men and 1212 German women aged 40–69 yr; two cohorts: 8-yr and 5-yr follow-up, respectively.	Three indices (total physical activity, leisure-time physical activity, and conditioning physical activity) derived from energy expenditure estimates that include duration, frequency, and intensity estimates.	CVD mortality.	Inverse and null association. Null associations seen for total activity and leisure activity in men and women. Inverse association seen for conditioning and sports activity among men.	No/yes. Based on several indices of total energy expenditure.	Association limited to conditioning exercises and sports. No associations in women.
Bijnen et al. (1998) (4)	802 Dutch men aged 64–84 yr at baseline; 10-yr follow-up.	Physical activity index based on frequency and duration.	CVD death (ICD-9 402-444; N = 199)	Inverse association across tertiles of physical activity index (P for trend < 0.05)	Yes. Based on total physical activity.	Association remained after controlling for confounding variables.
Sesso et al. (1999) (45)	1564 college alumnae, average age of 45.5 yr at baseline; followed from 1962–1993 (average of 22.4 years of follow-up).	Physical activity index (kcal·wk^{-1}) estimated from reports of stairs climbed, city blocks walked and sports play each week.	Self-reported CVD incidence and mortality (N = 131 nonfatal and 50 fatal).	Inverse association. Risk estimates across three categories of physical activity successively lower with higher activity. Point estimates not different from unity.	Yes. Based on intensity and frequency.	No statistical significance to trend and effect apparently confined to reported walking activity (blocks walked)

CI, confidence interval; RR, relative risk; ICD, International Classification of Diseases.

"U"-shaped relation with a successively higher relative risk of CHD evident at the highest physical activity levels investigated (4,48).

The bulk of the existing scientific work on physical activity and cardiovascular disease has focused on CHD as the outcome. Since the earliest studies among London busmen (32), techniques for measuring physical activity have become more sophisticated, more populations have come under observation, and follow-up experience has grown. As stated previously, other, more methodologically rigorous reviews (2,39) have concluded that physical activity is causally and inversely related to CHD risk.

TABLE 2. Population-based studies of association of physical activity as related to coronary heart disease (CHD): English literature, 1953–August 2000.

Study	Population	Definition of Physical Activity	Definition of Coronary Heart Disease	Main Findings	Dose Response	Comments
Morris and Crawford (1958) (31)	3731 case necropsy studies (age 45–70 yr) conducted by participating pathologists in Scotland, England and Wales National Health Service.	Physical activity at work defined by coding of last known job title before death (light, active, heavy).	Necropsy evaluation of ischemic myocardial fibrosis among noncoronary deaths.	Inverse association. Relative risk for noncoronary death for persons occupied in light occupations was 1.97 compared with those in heavy group. Active group rate was between estimates for light and heavy.	Yes. Based on job title.	No confounding control, but one of few pathology studies. Although outcome was noncoronary disease deaths, results were similar in subgroup of men who died of conditions associated with CHD.
Taylor et al. (1962) (53)	191,609 white male railroad industry employees aged 40–64 yr with at least 9.5 yr of service; 136,109 man-years.	Physical activity at work defined by job title. Jobs were defined as clerks, switchmen, and section men.	Death due to arteriosclerotic disease (ICD 420, 422) in 1955–1956.	Inverse association. Relative risk for arteriosclerotic disease among clerks was 2.03 relative to section men. Risk estimate for switchmen was 1.46.	Yes. Based on job title.	No confounding control. Results in 5-yr age categories (age-specific analyses) were consistent with overall results.
Paffenbarger and Hale (1975) (33)	6351 San Francisco Bay Area longshoremen aged 35–74 yr, followed for 22 yr, death, or age 75 from 1951.	Work-years according to job category of jobs requiring heavy (5.2–7.5 kcal·min^{-1}), moderate 2.4–5.0 kcal·min^{-1}), and light (1.5–2.0 kcal·min^{-1}) levels of energy output.	CHD death (ICD-7 420) (N = 598).	Inverse association. Relative to heavy category, age-adjusted risks of CHD death in moderate and light categories were 1.7 and 1.8, respectively.	Yes. Based on job title.	Efforts made to evaluate job changes in the cohort over time. No confounding variable control.
Paffenbarger et al. (1977) (34)	3686 San Francisco Bay Area longshoremen aged 35–74 yr and followed for 22 yr death, or age 75 from 1951.	Work-years by category of job requiring high (5.2–7.5 kcal·min^{-1}), intermediate 2.4–5.0 kcal·min^{-1}), and light (1.5–2.0 kcal·min^{-1}) levels of energy output.	CHD death (ICD-7 420) (N = 395).	Inverse association overall, inverse for younger birth cohorts and null for older cohorts. Overall relative to high category, age-adjusted risks of CHD death in intermediate and light categories were 1.8 and 1.6, respectively.	No/yes. Based on job title.	When birth cohorts analyzed individually, dose-response only noted in age-adjusted rates for two younger groups. Two older groups exhibited no association.
Rosenman et al. (1977) (42)	2065 white male San Francisco Bay Area United States federal employees aged 35–59 yr, and followed for 4 yr.	Work physical activity based on job classification, estimated caloric expenditure for work activity, estimated caloric expenditure for nonwork activity.	Fatal and nonfatal CHD (N = 65).	Null association. No apparent association between physical activity indices and CHD.	No. Based on intensity and frequency.	Relatively short-term follow-up.
Paffenbarger et al. (1978) (36)	16,936 Harvard male alumni aged 35–74 yr and followed for 6–10 yr.	Kilocalorie energy expenditure index (kcal·wk^{-1}) based on self-report of stairs climbed, blocks walked, and strenuous sports play.	Fatal and nonfatal first heart attack (N = 572).	Age-adjusted relative risk of first heart attack for group who expended fewer than 2000 kcal·wk^{-1} based on physical activity index was 1.64 compared with similar men who expended 2000 or more kcal·wk^{-1}.	Yes. Based on intensity and frequency.	History of athleticism was not associated with lower risk unless there was current and energy expenditure as well.
Garcia-Palmieri et al. (1982) (10)	8793 Puerto Rican men aged 45–64 yr, followed for up to 8.25 yr.	Usual 24-h physical activity index based on h·d^{-1} at specific intensity.	CHD incidence other than angina pectoris (N = 335).	Inverse association. Physical activity index was significantly related to lower risk of CHD in urban as well as rural-dwelling men.	Yes. Based on duration and intensity.	
Paffenbarger et al. (1984) (35)	16,936 male college alumni who entered college between 1916 and 1950; followed from 1962–1978.	Physical activity index (kcal·wk^{-1}) estimated from reports of stairs climbed, city blocks walked and sports play each week.	Death due to CHD (N = 441).	Inverse association. Relative to highest category of index (2000+ kcal·wk^{-1}), risk estimates in next two lower categories were 1.28 and 1.84, respectively.	Yes. Based on intensity and frequency.	Significant dose-response trend after adjusting for differences in age, cigarette smoking, and hypertension prevalence.

TABLE 2. *Continued*

Study	Population	Definition of Physical Activity	Definition of Coronary Heart Disease	Main Findings	Dose Response	Comments
Menotti and Seccareccia (1985) (28)	99,029 Italian male railroad employees aged 40–59 yr; followed for 5 yr.	Classification of occupational physical activity (heavy, moderate, sedentary).	Fatal myocardial infarction (N = 614).	Inverse association. Relative to sedentary category, men in moderate and heavy occupational activity categories had risks of 0.97 and 0.64, respectively.	Yes. Based on job classification.	Age-adjusted only.
Kannel et al. (1986) (17)	1166 Framingham men aged 45–64 yr; 24 hr of follow-up.	Physical activity index based on hours per day at activity-specific intensity. Occupational physical activity classified by physical demand of work.	Death due to CHD (N = 220).	Inverse association. For physical activity index, age-adjusted RR (relative to high category) = 1.38 (low), 1.21 (moderate). For occupational activity, age-adjusted RR (relative to heavy category) = 1.27 (sedentary), 1.22 (light), 0.99 (medium).	Yes. Based on duration and intensity.	Inverse association constant across all analyses. Inverse association maintained after multivariate confounding control.
Leon et al. (1987) (25)	12,138 North American men at high risk for CHD, aged 35–57 yr; followed for average of 7 yr.	Leisure-time physical activity index with intensity codes per activity to approximate energy expenditure ($min \cdot wk^{-1}$).	Fatal and nonfatal CHD (N = 781; 368 fatal).	Inverse association. Multivariate adjusted risk estimate (relative to low activity tertile) for tertiles II and III were 0.90 (95% CI = 0.76–1.06) and 0.83 (95% CI = 0.70–0.99), respectively.	Yes. Based on frequency, intensity, and duration.	Dose response for fatal and nonfatal cases combined. No dose-response for CHD death or sudden death alone.
Sobolski et al. (1987) (51)	2109 Belgian men aged 40–55 yr in 1976–1978 and followed for 5 yr.	Questionnaire assessment of physical activity on the job and during leisure time.	Incident cases of fatal and nonfatal myocardial infarction and sudden death (N = 36).	Null association for both leisure time and occupational physical activity.	No	One of two studies to simultaneously evaluate associations of physical activity, physical fitness, and CHD. Inverse association between physical fitness and CHD. Small number of cases.
Donahue et al. (1988) (6)	7644 Hawaiian men of Japanese ancestry aged 45–64 yr with no history of heart disease; 12-yr follow-up.	Self-report of 24-h habitual physical activity in 1965–1968; 3-point scale defined by tertiles of distribution.	Incident cases of fatal and nonfatal CHD (N = 444).	Inverse association. RR among active men relative to sedentary men was 0.69 (95% CI 0.53–0.88) for participants aged 45–64 and 0.43 (95% CI 0.19–0.99) for older participants aged 65–74.	Yes. Based on crude classification of frequency.	Adjusted for age, alcohol use, and smoking status.
Johansson et al. (1988) (16)	7495 Göteburg men aged 47–55 yr at entry and followed for an average of 11.8 yr.	Physical activity at work (4-point scale) and physical activity during leisure time (4-point scale).	Incident cases of fatal and nonfatal CHD.	Null association between physical activity at work and CHD risk. Inverse association (not statistically significant) between leisure time physical activity and CHD.	No. Based on job classification and combination of leisure intensity and frequency.	Extensive confounding variable control. Ancillary analysis on postinfarction patients also yielded null association.
Slattery et al. (1989) (50)	3043 male United States railroad employees followed for 17–20 yr.	Leisure-time physical activity index with intensity codes per activity to approximate energy expenditure ($kcal \cdot wk^{-1}$).	CHD mortality (ICD-8 410-414).	Inverse association. Adjusted risk estimate (relative to highest physical activity category) was 1.28 for sedentary group.	Yes. Based on frequency, intensity, and duration.	Risk estimate adjusted for baseline age, systolic blood pressure, smoking status, and serum cholesterol. Point estimate for sedentary group not different than unity.
Morris et al. (1990) (30)	9376 male British middle grade executives aged 45–64 yr and free of known coronary disease; followed for an average of 9.3 yr.	Leisure-time physical activity reported over previous 4 wk. Energy expenditure values (metabolic equivalents) ascribed to reported activities.	Fatal and nonfatal CHD (ICD 410-414) (N = 474).	Inverse association. Age-adjusted risk of combined fatal and nonfatal CHD for 3 episodes per week of vigorous physical activity, relative to sedentary group was 0.36.	Yes. Based on frequency, intensity, and duration.	Association only noted for "vigorous" physical activity. No association with nonvigorous physical activities. No confounding adjustment.

TABLE 2. *Continued*

Study	Population	Definition of Physical Activity	Definition of Coronary Heart Disease	Main Findings	Dose Response	Comments
Lindsted et al. (1991) (26)	9484 Seventh-day Adventist men aged 30 yr and over; 26-yr follow-up.	Self-report to single physical activity question.	Ischemic heart disease mortality (ICD-8 410-414) (N = 1351).	Null association. Risk estimates of CHD death exhibited a U-shaped relationship with increasing physical activity levels.	No. Based on single question of self-ascribed intensity.	Possible protective association among moderate activity group.
Shaper and Wannamethee (1991) (48)	7735 British men aged 40–59 yr; 8.5-yr follow-up.	Self-report of physical activity at baseline. Six-point scale defined based on type and frequency of activity.	Fatal and nonfatal heart attack (N = 488)	Inverse association. Among men with no preexisting heart disease significant inverse trend between was observed. Relative to sedentary group, risks in the next five groups were: II 0.9 (95% CI = 0.5–1.3), III 0.9 (95% CI = 0.6–1.4),), IV 0.5 (95% CI = 0.2–0.8),), V 0.5 (95% CI = 0.3–0.9),), VI 0.9 (95% CI = 0.5–1.8)	No. Based on frequency and intensity.	No clear linear trend observed in men with or without existing ischemic heart disease. Apparent threshold association middle of physical activity distribution. Upturn in CHD death rates noted at highest level of physical activity.
Seccarecia and Menotti (1992) (44)	1712 men from Northern and Central Italy, aged 40–59 yr, initially examined in 1960 and followed for 25 yr.	Physical activity at work (self-report) classified as sedentary, moderate, and heavy.	Death due to CHD	Inverse association. Age-adjusted RR for moderate and heavy categories, compared with sedentary group was 1.44 and 1.70, respectively.	Yes. Based on job classification.	Inverse association remained statistically significant after confounding adjustment.
Shaper et al. (1994) (47)	5694 British men aged 40–59 yr; 9.5-yr follow-up.	Self-report of physical activity at baseline. Six-point scale defined based on type and frequency of activity. Data analyzed by stratum of hypertensive status.	Fatal and nonfatal heart attack (N = 311; 165 normotensive, 146 hypertensive).	Inverse association (statistically significant trend) among nonhypertensive participants, U-shaped association among hypertensive participants.	Yes/no. Based on frequency and intensity.	Previously reported upturn in CHD death rates noted at highest level of physical activity may be attributed to interaction of vigorous physical activity and hypertension.
Rodriguez et al. (1994) (40)	7074 Hawaiian men of Japanese ancestry aged 45–68 yr; 23-yr follow-up.	Self-report of 24-hr habitual physical activity in 1965–1968. Three-point scale defined based on tertiles of distribution.	Incident cases of fatal and nonfatal CHD (N = 340).	Null association. RR for tertiles of physical activity index for all CHD = (low) 1.0, (moderate) 1.07 (95% CI = 0.90–1.26), and (high) 0.95 (0.80–1.14).	No. Based on duration and intensity.	
Lemaitre et al. (1995) (24)	268 case and 925 comparison postmenopausal women from a U.S. health maintenance organization; average age 66.9 yr.	Self-report of 30-d physical activity prior to event. Energy expenditure estimated from reported intensity, duration, and frequency.	Incident nonfatal myocardial infarction between July 1986 and December 1991 (N = 268).	Inverse association. Relative to lowest quartile of energy expenditure, odds ratios (95% CI) for three highest quartiles were: 0.52 (0.34–0.80), 0.40 (0.26–0.63), 0.40 (0.25–0.63).	Yes. Index of energy expenditure based on frequency, intensity, and duration.	Extensive confounding variable controls. Similar findings for energy expended in nonstrenuous leisure-time physical activity.
Folsom et al. (1997) (9)	7852 women and 6188 men from North America, aged 45–64 yr at baseline; multiracial population; 4 to 7-yr follow-up.	Self-report of habitual physical activity combined into three indices (work, leisure, and sports), all on a 5-point scale.	Incident cases of fatal and nonfatal CHD (women N = 97; men N = 223).	Inverse association. Clearest trends evident for sport and leisure indices of physical activity. Work index showed null association.	Yes/no. Based on frequency, intensity, and duration.	Extensive confounding control. No association seen in black participants for any index.

Studies published since those reviews do not provide any indication to conclude otherwise. Physical activity is inversely related to risk of CHD, and the bulk of the observational studies suggest this inverse relation to be a dose response.

Stroke. Stroke incidence and mortality is a major public health problem in developed countries. Atherosclerosis of the extra- and intracranial arteries is thought to be the general underlying pathologic basis of both CHD and thromboembolic (ischemic) stroke. Hypertensive disease, although a risk factor for CHD and thromboembolic stroke, is thought to be the major pathologic determinant of hemorrhagic stroke. A review of physical activity, physical fitness, and stroke has been published (21). A

TABLE 2. *Continued*

Study	Population	Definition of Physical Activity	Definition of Coronary Heart Disease	Main Findings	Dose Response	Comments
Haapanen et al. (1997) (11)	1340 men and 1500 women from northeastern Finland, aged 35–63 yr at baseline; 10-yr follow-up.	Total energy expenditure based on self-reports of frequency and duration of activities with an assumed intensity.	Fatal and nonfatal (self-reported) CHD (N = 108 men, N = 75 women).	Inverse relation for men, point estimates all include unity. Null association for women.	Yes for men, no for women. Based on frequency, intensity, and duration.	More vigorous activity associated with lower risk of CHD in men but not women.
Rosengren and Wilhelmsen (1997) (41)	7142 Swedish men aged 47–55 yr at baseline; 20-yr follow-up.	Self-reported indices of occupational and leisure-time physical activity (4-point scales).	Death due to CHD (N = 672).	Null association with occupational physical activity. Inverse association with leisure physical activity but no additional benefit past moderate activity.	No. Based on intensity above minimal frequency per week.	Long-term follow-up and confounding variable control.
Bijnen et al. (1998) (4)	802 Dutch men aged 64–84 yr at baseline; 10-yr follow-up.	Physical activity index based on frequency and duration.	CHD death (ICD-9 410-414) (N = 90).	Null association. Suggestion of U-shaped relation with tertiles of physical activity index.	No. Based on total physical activity (frequency and duration).	Adjusted for age, cigarette smoking, and alcohol consumption.
Wannamethee et al. (1998) (56)	5567 British men aged 52–72 yr at baseline; 3-yr follow-up.	Physical activity index based on frequency and intensity. Six categories formed from index.	Fatal and nonfatal CHD. Fatal coded to ICD-9 410-414. WHO criteria used for nonfatal (N = 92).	Inverse association. Men who became active reduced their risk of mortality by 33.3% (RR = 0.66, 95% CI = 0.35–1.23).	Yes. Based on changes in physical activity index between two points in time.	Short follow-up. Similar findings among men with preexisting heart disease.
Kaprio et al. (2000) (19)	8205 Finnish men aged 25–69 yr at baseline; 18-yr follow-up.	Three level physical activity index based on reported frequency, intensity and duration of activity.	Fatal and nonfatal CHD incidence prior to 70 yr (ICD 410-414) (N = 723).	Inverse association. Relative to sedentary men, lowest adjusted point estimate seen for most active group (conditioning exercisers RR = 0.68, 95% CI 0.50–0.92). RR for occasional exercisers was 0.84 (95% CI = 0.70–1.01).	Yes. Based on total physical activity.	No association with occupational physical activity.
Stampfer et al. (2000) (52)	84,129 U.S. female registered nurses aged 30–55 yr at baseline; 14-yr follow-up.	Self-report of time per week spent in moderate-to-vigorous physical activity; 5-point scale.	Fatal and nonfatal coronary events between 1980 and 1994 (N = 1128; 296 CHD deaths).	Inverse association. Highest point estimate in least active group (1.41, 95% CI 1.15–1.75). All other point estimates include unity.	Yes. Based on frequency above minimal intensity.	Extensive confounding variable control.
Sesso et al. (2000) (46)	12,516 male college alumni (aged 39–88 yr) who entered college between 1916 and 1950; followed from 1977–1993.	Physical activity index ($kJ \cdot wk^{-1}$) estimated from reports of stairs climbed, city blocks walked, and sports play each week (in 1977).	Fatal and nonfatal (self-report) CHD (N = 2135).	Inverse association. Relative to highest category of index ($<2100+$ $kJ \cdot wk^{-1}$), age-adjusted risk estimates in next four successively higher categories were 0.85, 0.75, 0.73, and 0.73, respectively (P for trend < 0.001).	Yes. Based on intensity and frequency.	Significant dose-response trend after multivariate adjustment. Association present for vigorous activities but not light or moderate.
Lee et al. (2000) (23)	7307 male college alumni (average age 66.1 yr) who entered college between 1916 and 1950; followed from 1988–1993.	Physical activity index ($kJ \cdot wk^{-1}$) estimated from reports of stairs climbed, city blocks walked, and sports play each week (in 1988).	Fatal and nonfatal (self-report) CHD (N = 482).	Inverse association. Relative to highest category of index ($<4200+$ $kJ \cdot wk^{-1}$), multivariate risk estimates in next four successively higher categories were 0.80, 0.80, 0.74, and 0.62, respectively (P for trend = 0.046).	Yes. Based on intensity, duration, and frequency.	Longer durations of physical activity are not associated with lower risk of CHD once total energy expenditure is taken into account.

CI, confidence interval; RR, relative risk.

summary of literature of population-based observational studies of physical activity as they relate to stroke as an outcome is highlighted in Table 3.

The published literature from population-based observational studies relating physical activity to risk of CVA closely parallels that of CVD and CHD in terms of designs and populations under observation. Fifteen major studies (16 separate publications) that provide evidence toward evaluation of a physical activity dose–stroke response are available for review. Of these, four have analyzed the rela-

tion among women (14,15,20,43). Two of the 15 studies on physical activity and stroke were of a case-comparison design (14,43), with the remaining 13 being prospective, cohort studies with follow-up periods between 5 and 26 yr. Seven studies concentrated on fatal stroke as outcomes, one exclusively on nonfatal stroke and the remainder on a combination of fatal and nonfatal outcomes.

Six of the studies were judged to provide evidence of a dose-response relation (18,35,14,43,15,55), eight studies provided no support for a dose-response relation (4,7,10,12,22,26,27,41), and two provided mixed support (varying results in separate subanalyses) (1,20). Strikingly, several studies reported prominent "U"-shaped distributions of the relation between physical activity and risk of stroke (7,22,26,28).

Taken together, these findings suggest a questionable dose-response association between physical activity and risk of stroke. Indeed, they raise the question of the presence of any form of inverse association. Several of the studies are unable to separate out various subtypes of stroke (hemorrhagic vs occlusive). The importance of this observation lies in the fact that the pathophysiology of the two types of stroke is very different, and it is possible that physical activity may be differentially related to one type (occlusive) and not the other. Moreover, as with the CVD literature, all studies relate physical activity measured at baseline to stroke outcomes that are measured sometimes many years in the future. No studies have presented information on behavioral changes in physical activity and how that may relate to the change in the risk of stroke over time.

Physical activity is causally and inversely related to the risk of death due to CHD. A variety of mechanisms are available to explain this phenomenon. Given the probability of common pathophysiologic mechanisms in CHD and ischemic stroke, namely atherosclerosis, it follows that physical inactivity would also adversely affect the risk of stroke. Moreover, physical activity is known to indirectly do so and to positively be associated with blood pressure, clotting factors, glucose tolerance, and smoking habits (54), all factors that have been associated with increased risk of stroke. Although attractive as a hypothesis, the currently available data are equivocal concerning the role that physical activity may play in the risk of stroke. Existing studies do not show the consistencies noted in the association that are seen for CVD and CHD and do not support the conclusion of a dose-response relation.

SUMMARY AND FUTURE RESEARCH PRIORITIES

Physical activity appears to be inversely associated with the risk of CVD and specifically CHD in a dose-response fashion. The strength and the consistency of the evidence that has accumulated over the years has lead others to conclude that physical activity is causally linked to the incidence of CVD and particularly CHD. The evidence summarized in this review, including recent studies, supports those conclusions. Although the results of individual studies are variable in terms of point estimates of risk, the pattern that emerges when studies are taken together, is one of lower risk of CVD with ensuing higher levels of physical activity.

The role that physical activity may play in the risk of stroke is not as clear however. Although stroke is a cardiovascular disease, a much larger proportion is attributable to CHD. Therefore, the discrepant results seen among studies of CVD and CHD and studies of stroke may be attributed to the large proportion of CVD that is actually CHD in origin. When CHD and stroke are studied individually, the inverse association is readily apparent for CHD but not for stroke. Many studies designed to detect a dose-response gradient have been unable to do so, and there is some suggestion of a nonlinear, "U-shaped" relation. More work is needed to determine if physical activity is similarly related to risk of stroke as it is to risk of CHD.

Several unresolved issues are apparent when considering the relation between physical activity and cardiovascular disease. First, is physical activity, physical fitness, or some combination of both related to risk of CVD and CHD? Although physical activity is a behavior, it has many physiological effects on the circulatory, metabolic, and musculoskeletal systems. Most studies have used physical activity measures rather than fitness, and only two studies have jointly assessed both (13,51). The crudeness of existing physical activity measures as well as the genetic contributions to physical fitness continue to plague existing research. More work, with better measures of physical activity and joint measurement of physical fitness, is necessary to help quantify the environmental versus genetic contributions to reduced risk of CVD and CHD.

Second, there are few data on changes in physical activity or physical fitness as they relate to CVD risk. All studies but one (56) have relied on a single, baseline measure of physical activity or fitness and related that measure to risk of CVD or CHD sometime in the future. Follow-up periods in existing studies extend up to 26 yr. It is therefore more difficult to interpret these long-term follow-up studies without some measure of change during the course of the study. Behavioral changes and changes in health status and the like are more likely to occur with longer periods of follow-up observation, and, without an assessment other than that which was taken at baseline, there is a substantial probability that misclassification will occur.

There are no population-based observational studies that address the appropriate physical activity profile necessary to reduce the risk of CVD. There is convincing evidence of a dose-response relation between physical activity and/or physical fitness and risk of CVD and CHD in the populations studied. This has been translated in current recommendations that moderate intensity physical activity is sufficient to provide reduced risk of CVD and CHD (37). What is unavailable, however, is an assessment of the optimal way for which that dose should be accumulated (i.e., type, intensity, frequency of bouts, duration of bouts, and various interactions). There is no evidence that accumulation of a total dose of physical activity over an extended period of time at a relatively low intensity provides any protection

TABLE 3. Population-based studies of association of physical activity as related to stroke (CVA): English literature, 1953–August 2000.

Study	Population	Definition of Physical Activity	Definition of Stroke	Main Findings	Dose Response	Comments
Kannel and Sorlie (1979) (18)	1909 Framingham (U.S.) men aged 35–64 at fourth biennial examination; 14-yr follow-up.	Physical activity index based on hours per day spent at activity-specific intensity.	Cerebrovascular accident (N = 87).	Inverse association (statistically nonsignificant) between physical activity index and 14 year incidence of stroke.	Yes. Based on duration and intensity.	No statistical significance after controlling for several confounding variables.
Herman et al. (1983) (14)	132 hospital-based Dutch stroke cases and 239 age- and sex-matched controls; men and women aged 40–74 yr.	Leisure time physical activity (greatest portion of one's lifetime) ranging from little to regular-heavy.	Rapidly developed clinical signs of focal or global disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than vascular origin.	Inverse association. Relative to lowest physical activity category, risk estimates for moderate and high categories were 0.72 (95% CI = 0.37–1.42) and 0.41 (95% CI = 0.21–0.84).	Yes.	Adjusted for a variety of potential confounding influences.
Paffenbarger et al. (1984) (35)	16,936 male college alumni who entered college between 1916 and 1950; followed from 1962–1978.	Physical activity index (kcal·wk^{-1}) estimated from reports of stairs climbed, city blocks walked and sports play each week.	Death due to stroke (N = 103).	Inverse association. Relative to highest category of index (2000+ kcal·wk^{-1}), risk estimates in next two lower categories were 1.25 and 2.71, respectively.	Yes. Based on intensity and frequency.	Significant dose-response trend after adjusting for differences in age, cigarette smoking and hypertension prevalence.
Menotti and Seccareccia (1985) (28)	99,029 male Italian railroad employees aged 40–59 yr; followed for 5 yr.	Classification of occupational physical activity (heavy, moderate, sedentary).	Fatal stroke (N = 187).	Nonlinear U-shape association. Relative to sedentary category, men in moderate and heavy occupational activity categories had risks of 0.65 and 1.0, respectively.	No. Based on job classification.	Age-adjusted only.
Menotti et al. (1990) (27)	8287 men aged 40–59 yr in six of seven countries from Seven Countries Study; 20-yr follow-up.	Classification of occupational physical activity (heavy, moderate, sedentary).	Fatal stroke (cohort analysis).	Null association.	No. Based on job classification.	No association after statistical adjustment for risk factors.
Harmsen et al. (1990) (12)	7495 Swedish men aged 47–55 yr at baseline examination; followed for average 11.8 yr.	Physical activity at work and leisure hours (low, high).	Fatal stroke (all and subtypes) (N = 230)	Null association. Relative to low physical activity category, slightly elevated, but not statistically significant risk estimates were observed for all strokes and subtypes for high activity group.	No.	No association after statistical adjustment for risk factors.
Lindsted et al. (1991) (26)	9484 male Seventh-day Adventists aged 30 yr and older; 26-yr follow-up.	Self-report of physical activity level in 1960 (highly active, moderately active, low activity).	Fatal stroke (N = 410).	Nonlinear U-shape association. Relative to low activity level, risk estimates for moderate activity were 0.78 (95% CI = 0.61–1.00) and for high activity were 1.08 (95% CI = 0.58–2.01).	No. Based on single question of self-ascribed intensity.	Adjusted for race, smoking status, education, medical illness, BMI, marital status, and dietary pattern.
Wannamethee and Shaper (1992) (55)	7735 British men aged 40–59 yr; 8.5-yr follow-up.	Self-report of physical activity at baseline; 6-point scale defined based on type and frequency of activity.	Fatal and nonfatal stroke (N = 128).	Inverse association. Statistically significant linear trend of lower risk of stroke with higher physical activity scale.	Yes. Based on frequency and intensity.	Linear trend observed in men both with and without existing ischemic heart disease.
Abbott et al. (1994) (1)	7530 Hawaiian men of Japanese ancestry aged 45–68 yr; 22-yr follow-up.	Self-report of 24-h habitual physical activity in 1965–1968; 3-point scale defined (inactive, partially active, active).	Fatal and nonfatal neurologic deficit with sudden occurrence and remaining present for at least 2 wk or until death (subtypes) (N = 537).	Null association seen for all strokes and all subtypes for men aged 45–54 yr. Inverse association seen for all strokes and subtypes for men aged 55–68 yr.	Yes in older. No in younger. Based on duration and intensity.	No association of physical activity to risk of stroke in older smokers.

against an increased risk of CVD or CHD although recent work (44) suggests that, after controlling for total energy expenditure, the duration of the exercise session becomes less important in predicting CHD risk. More work is needed to determine the type of exercise dose that is necessary for various population subgroups.

Studies in women and minority groups are glaringly lacking. Initial cohort studies of CVD and CHD were begun in white men because of the disproportionate disease burden in men compared with women as well as for convenience. The inertia of tradition apparently has made it difficult to gather similar data in women and blacks, Hispanics, and Asians.

TABLE 3. *Continued*

Study	Population	Definition of Physical Activity	Definition of Stroke	Main Findings	Dose Response	Comments
Kiely et al. (1994) (20)	Four cohorts of Framingham men and women. Cohort I, 1897 men aged 35–69 yr. Cohort II, 2299 women aged 35 and 68 yr. Cohort III, men aged 49–83 yr. Cohort IV, women aged 49–83 yr. Follow-up for Cohorts I and II = maximum of 32 years. Follow-up for Cohorts III and IV = maximum of 18 years.	Self-report of daily activity level. Composite score formulated from index and categorized into high, medium, and low physical activity.	Fatal and nonfatal first occurrence of atherothrombotic brain infarction, cerebral embolism, or other type of stroke. Cohort I, *N* = 195, Cohort II, *N* = 232, Cohort III *N* = 113, Cohort IV *N* = 140.	Cohort I: Nonsignificant inverse association: relative to low physical activity group, risk estimate for medium group = 0.90 (0.62–1.31) and high group = 0.84 (0.59–1.18). Cohort II: Nonsignificant nonlinear association: medium group = 1.21 (0.89–1.63), high group = 0.89 (0.60–1.31). Cohort III: Significant inverse association: medium group = 0.41 (0.24–0.69), high group = 0.53 (0.34–0.84). Cohort IV: Nonsignificant nonlinear association: medium group = 0.97 (0.64–1.47), high group = 1.21 (0.75–1.96).	Yes, C I No, C II Yes, C III No, C IV Based on duration and intensity.	Control for many confounding factors. Nonlinear association in women only (Cohorts III and IV). Suggestion of threshold relationship in Cohort III.
Rosengren and Wilhelmsen (1997) (41)	7142 men aged 47–55 yr at baseline; 20-yr follow-up.	Self-reported indexes of occupational and leisure-time physical activity (both 4-point scales).	Death due to stroke (*N* = 111).	Null association with both occupational physical activity and leisure physical activity. Suggestion of U-shaped relation with leisure index (nonsignificant).	No. Indices based on intensity above minimal frequency per week.	Long-term follow-up and confounding variable control.
Bijnen et al. (1998) (4)	802 Dutch men aged 64–84 yr at baseline; 10-yr follow-up.	Physical activity index based on frequency and duration.	Cerebrovascular accident death (ICD-9 430-438; *N* = 47).	Inverse association. Relative to least active tertile, adjusted point estimates for middle and most active tertiles were: 0.65 (95% CI, 0.33–1.25) and 0.55 (0.24–1.26), respectively.	No. Nonstatistically significant trend across tertiles. Based on frequency and duration.	Adjusted for age, smoking habit, and alcohol consumption.
Lee and Paffenbarger (1998) (22)	11,130 male college alumni who entered college between 1916 and 1950; followed from 1977–1990; average age 58 yr.	Physical activity index (kcal·wk^{-1}) estimated from reports of stairs climbed, city blocks walked and sports play each week. Indices of total energy expenditure and intensity.	Fatal and nonfatal incident stroke (*N* = 378).	Null association. U-shaped distribution evident for most indices; most pronounced with index of total energy expenditure. Point estimates for most quantiles of indices were not different than unity.	No. Indices based on frequency, intensity, and duration, as well as individual activities.	Extensive control for confounding variables.
Sacco et al. (1998) (43)	369 case (*N* = 206 women) and 678 comparison (*N* = 394 women) participants; average age 69.9 yr.	Self-report of frequency and duration of participation in defined list of physical activities of predefined intensity.	Nonfatal ischemic stroke incident cases (*N* = 369) between July 1993 and December 1995.	Inverse association. Relative to inactive referent, indices of both intensity of activity and duration of activity were associated with being a stroke case ($P = 0.006$).	Yes. Based on intensity and duration.	Dose response relations were also observed for age, gender, and ethnicity strata.
Evenson et al. (1999) (7)	8296 women and 6279 men aged 45–64 yr at baseline; multiracial population; average 7.2-yr follow-up.	Self-report of habitual physical activity combined into three indices (work, leisure, and sports) all on a 5-point scale.	Fatal and nonfatal ischemic stroke (*N* = 189).	Mixed findings. Null associations with sport index; U-shaped (nonsignificant) relation with leisure index; U-shaped (significant) relation with work index.	No. Based on intensity and frequency.	Extensive confounding control. No ethnic- or sex-specific analyses conducted.
Hu et al. (2000) (15)	72,488 female nurses aged 40–55 yr at baseline; 8-yr follow-up.	Self-report of time per week spent in moderate-to-vigorous physical activity. Quintile categories based on MET hours per week.	Fatal and nonfatal stroke between 1986 and 1994 (*N* = 407; 258 ischemic; 67 subarachnoid hemorrhage; 42 intracerebral hemorrhage; 40 unknown).	Inverse association. Significant trend for ischemic stroke ($P < 0.001$). Point estimates in top 3 of 5 physical activity categories significantly different from unity. No association for other subtypes of stroke.	Yes. Frequency above minimal intensity. Subanalyses suggested additional dose-response by walking intensity (independent of frequency).	Extensive confounding variable control. Change in physical activity between 1980 and 1986 was associated with a 29% lowering of the risk of ischemic stroke.

CI, confidence interval; RR, relative risk.

Such data are critical to complete our understanding and to provide appropriate, more targeted, intervention efforts. Despite the dose-response relation observed for physical activity and CVD and CHD, these data are largely gathered from observations among white men. Further study in women and other ethnic groups may reveal different pat-terns to the association such as a threshold or nonlinear relation.

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Exercise characteristics and the blood pressure response to dynamic physical training

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ABSTRACT

FAGARD, R. H. Exercise characteristics and the blood pressure response to dynamic physical training. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., pp. S484–S492, 2001. **Purpose:** The purpose of this study was to assess the influence of the characteristics of the exercise program, particularly exercise intensity, on the blood pressure response to dynamic physical training in otherwise healthy normotensive and hypertensive subjects. **Methods:** This study is a meta-analysis of randomized controlled intervention trials and a description of studies in which different training regimens have been compared. **Results:** The weighted net reduction of blood pressure in response to dynamic physical training averaged 3.4/2.4 mm Hg ($P < 0.001$). Interstudy differences in the changes in pressure were not related to weekly frequency, time per session, or exercise intensity, which ranged from approximately 45–85%; these three characteristics combined explained less than 5% of the variance of the blood pressure response. The response of diastolic blood pressure was not different according to training intensity in studies that randomized patients to training programs with different intensities. Some studies reported a greater reduction of systolic blood pressure when intensity was about 40% than when participants exercised at about 70%, but this finding was not consistent, neither within nor between studies. **Conclusion:** Training from three to five times per week during 30–60 min per session at an intensity of about 40–50% of net maximal exercise performance appears to be effective with regard to blood pressure reduction. The evidence that higher intensity exercise would be less effective is at present inconsistent. **Key Words:** AEROBIC POWER, BLOOD PRESSURE, EXERCISE, EXERCISE INTENSITY, TRAINING PROGRAM

Weight reduction, salt restriction, moderation of alcohol consumption, and increased physical activity are generally accepted lifestyle measures for the management of hypertension (24,56). Whereas epidemiological studies suggest an inverse relationship between habitual physical activity and blood pressure (14,16), meta-analyses of controlled intervention trials concluded that adequate dynamic physical training contributes to the control of blood pressure (13,16,20). However, the optimal characteristics of the training program are still a matter of debate, particularly with regard to the intensity of exercise. In the present review we will address this question, first by analyzing relationships between exercise characteristics and blood pressure response across randomized controlled trials by use of meta-analytical techniques, and second by examining the results from studies in which different training regimens have been applied.

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METHODS

Selection of articles. Articles relevant to the aims of the present review were identified by a computer-assisted literature search and by checking the reference lists of published articles on the topic. The database used for the meta-analysis contains articles published before August 1998 (13) and the following criteria were applied with regard to their acceptability: randomized controlled trials of at least 4-wk duration concerning normotensive or hypertensive subjects, or both, in whom cardiovascular diseases were reasonably well excluded; random allocation to intervention groups and control groups or control phases in case of crossover design; full publication in a peer-reviewed journal; and absence of confounding by some other intervention during the intervention of interest. When the effects of different training programs were compared within studies, random allocation to the intervention groups or phases was required; however, a control group without intervention was not a prerequisite for inclusion. Finally, studies were accepted only when the actual blood pressures for the intervention and the control groups or phases, or the pressure changes during the intervention and control periods, were available.

Statistical analysis. Database management and statistical analyses were performed with the SAS software (SAS Institute, Inc., Cary, NC). Meta-analyses consisted of analyses of pooled data with study groups as the units of analysis, with weighting for the number of participants in each

group. The net effects of physical training were assessed by weighted pooled analyses of the changes in the intervention groups, adjusted for control data. Results are reported as weighted means and 95% confidence limits (95% CL). Finally, weighted metaregression analysis was applied to assess whether variations in the results were related to variations in study group or training characteristics (15).

RESULTS

Physical Training and Blood Pressure Control: Overall Results

We identified 44 randomized controlled trials on the effect of dynamic aerobic or endurance exercise on blood pressure at rest in otherwise healthy normotensive or hypertensive individuals (1–5,7–11,17–19,21–23,25–34,36, 37,39–49,51–55). Sixty-five percent of the 2674 participants were men. Nineteen studies comprised only men, four included only women, and the others included both sexes (or sex unknown in one). Some of these studies involved several groups of subjects or applied different training regimens in the same participants, so that a total of 68 training groups/programs are available for analysis. Average age of the groups ranged from 21 to 79 yr (median, 44). Duration of training involved 4 to 52 wk (median, 16). Training frequency ranged from one to seven sessions per week, but it is noteworthy that two thirds of the training programs applied three sessions per week and all but five programs three to five sessions per week. Each session lasted from 30 to 60 min in all but two programs (15 min), after exclusion of warm-up and cool-down activities (median exercise time, 40 min). The exercises involved walking, jogging, running in 69% of the studies, cycling in 50%, swimming in 3%, and other exercises were included in 23% of the training regimens. Average training intensity in the various groups varied between 30 and 87% of net maximal exercise performance (median, 65%). Exercise intensity was reported in percent of maximal oxygen uptake (3,5,9,19,33,43–45,53–55) or maximal work load (7,8,23,26,36,37,40) in 11 and seven of the 44 studies, respectively, and in percent of heart rate reserve (4,18,21,28,32,39,49,52) or maximal heart rate (1,2,10,11,17,22,25,27,29–31,34,42,47) in eight and 14 studies. Finally, two studies trained participants at the lactate threshold, which corresponded to approximately 50% of maximal oxygen uptake (48,51), and two did not give details on exercise intensity (41,46). When exercise intensity was expressed as a percent of maximal oxygen uptake or maximal heart rate, intensity was recalculated as percent of oxygen uptake reserve or heart rate reserve by accounting for resting oxygen uptake or heart rate, respectively (percent of net maximal exercise performance).

Table 1 summarizes the overall results. In the 68 study groups, the changes of blood pressure in response to training, after adjustment for the control observations, ranged from +9 to −20 mm Hg for systolic blood pressure and from +11 to −11 mm Hg for diastolic pressure. The overall net changes averaged −3.4/−2.4 mm Hg ($P < 0.001$), that is, after adjustment for control observations and after weighting for the number of trained participants who could be analyzed in each study group, their total number amounted to 1529. Baseline blood pressure was an important determinant of the blood pressure response. The training-induced weighted net change of blood pressure averaged −2.6 (95% CL, −3.7, −1.5)/−1.8 (95% CL, −2.6 −1.1) mm Hg in the 52 normotensive groups and −7.4 (95% CL, −10.5, −4.3)/−5.8 (95% CL, −8.0, −3.5) mm Hg in the 16 hypertensive groups. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg at baseline (24,56). Peak oxygen uptake increased significantly by 11.8% (95% CL, 10.3%, 13.4%), whereas heart rate and body mass index decreased, 6.8% (95% CL, 5.5%, 8.2%) and 1.2% (95% CL, 0.8%, 1.7%), respectively.

Evidence statement. Dynamic aerobic training reduces blood pressure. The blood pressure lowering effect is more pronounced in hypertensive than in normotensive subjects. Evidence Category A.

Influence of Training Characteristics

Across-study analysis. Thirty-five randomized controlled trials, comprising 45 study groups or interventions, applied only one training intensity, which ranged from 43–87% of net maximal exercise performance (median, 64%) (1–3,5,7–10,17,18,21–23,27–32,34,36,37,39,40,42–44,47–49,51–55). Figures 1 and 2 illustrate the relationships between the net changes in systolic and diastolic blood pressure, respectively, and net training intensity for the 45 study groups. Weighted single metaregression analysis showed that these relationships were significant for neither systolic ($y = -9.24 + 0.087 * x$; $r = 0.19$; $P = 0.21$) nor diastolic ($y = -2.56 - 0.004 * x$; $r = -0.01$; $P = 0.93$) blood pressure. The changes in blood pressure were not significantly related to the weekly training frequency ($P \geq 0.44$)

TABLE 1. Baseline data and net changes in response to training.

	Baseline		Net Change	
	N	Mean (95% CL)	Mean (95% CL)	*P* Value
Blood pressure (mm Hg)				
Systolic	68	126.2 (123.3, 129.0)	−3.4 (−4.5, −2.3)	<0.001
Diastolic	68	79.9 (77.9, 82.0)	−2.4 (−3.2, −1.6)	<0.001
Peak $\dot{V}O_2$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	59	31.4 (29.6, 33.2)	+3.7 (+3.2, +4.3)	<0.001
Heart rate ($beats \cdot min^{-1}$)	48	71.1 (69.3, 72.9)	−4.9 (−5.9, −3.9)	<0.001
BMI ($kg \cdot m^{-2}$)	64	25.6 (25.0, 26.1)	−0.34 (−0.46, −0.22)	<0.001

N, number of groups; $\dot{V}O_2$, oxygen uptake; BMI, body mass index.
Values are weighted means and 95% confidence limits (CL).

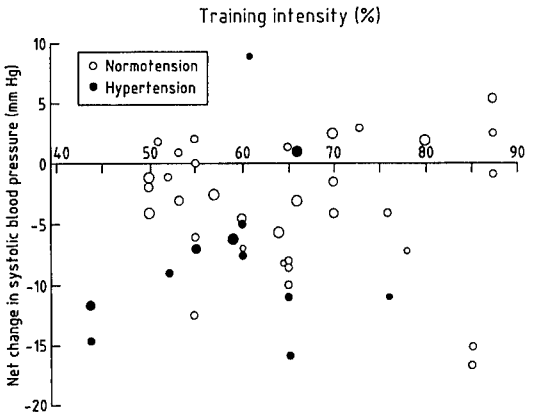


FIGURE 1—Changes in systolic blood pressure with training, adjusted for control data, versus training intensity, in normotensive (*open circles*) and hypertensive (*closed circles*) study groups. Training intensity is expressed as percent of maximal work load, heart rate reserve, or oxygen uptake reserve. The four sizes of the circles represent the number of analyzable trained subjects in each group, i.e., < 10, 10–19, 20–29, and ≥ 30, respectively. The weighted meta-regression coefficient r = 0.19 (P = 0.21).

or to the time per session ($P \geq 0.61$). Training frequency, time per session, and exercise intensity taken together explained 4.9% of the variance of the response of systolic blood pressure (P = 0.56) and 1.1% for diastolic blood pressure (P = 0.92). The total duration of the training program was a significant determinant of the response of systolic (r = 0.32; $P < 0.05$), but not of diastolic pressure (P = 0.37), the blood pressure reduction becoming less pronounced with longer program duration.

Within-study analysis. We identified 14 studies in which sedentary normal subjects (4,6,11,18,23,25,26) or hypertensive patients (19,33,35,38,40,45,50) were randomly allocated to different training programs, either in a parallel group or in a crossover design. The characteristics of the participants and of the training programs are summarized in Tables 2 and 3. Three studies assessed the influence of differences in weekly frequency, with identical remaining training characteristics (18,23,40). Eleven studies applied different exercise intensities, without changes in the other characteristics (6,33,38,45), or with differences in frequency, time per session, or type of exercises (4,11,19,25,26,35,50). Training frequency and/or time per session were usually lower in the higher intensity regimens. The results on blood pressure and on physical work capacity are given in Tables 4 and 5. Figures 3 and 4 illustrate the blood pressure changes in the studies that compared the effects of different exercise intensities regardless of differences in the other training characteristics.

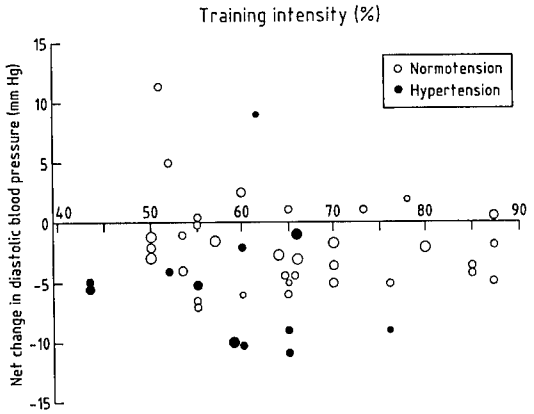


FIGURE 2—Changes in diastolic blood pressure with training, adjusted for control data, versus training intensity, in normotensive (*open circles*) and hypertensive (*closed circles*) study groups. Training intensity is expressed as percent of maximal work load, heart rate reserve, or oxygen uptake reserve. The four sizes of the circles represent the number of analyzable trained subjects in each group, i.e., < 10, 10–19, 20–29, and ≥ 30, respectively. The weighted metaregression coefficient r = 0.01 (P = 0.93).

Gettman et al. (18) examined the response of young normotensive men to running programs of 1-d, 3-d, and 5-d·wk^{-1} frequencies, 30 min per session, at 85–90% of heart rate reserve. Results indicated no significant blood pressure changes in any of the three groups in comparison with a recreational activity control group. Jennings et al. (23) found that training three times 30 min·wk^{-1} at 60–70% of maximal work load reduced supine blood pressure by 10/7 mm Hg, which was close to the response obtained with seven sessions per week (−12/−7 mm Hg). Nelson et al. (40) compared the results of three and seven exercise sessions per week in hypertensive patients. Training at the lower frequency reduced supine and standing blood pressure by 11/9 mm Hg and 12/11 mm Hg, respectively. The reductions were slightly but significantly ($P < 0.05$) more pronounced when subjects exercised seven times per week.

Duncan et al. (11) assessed the effects of aerobic walking (8 km·h^{-1}), brisk walking (6.4 km·h^{-1}), and strolling (4.8 km·h^{-1}) in sedentary premenopausal women. The participants walked 4.8 km·d^{-1} on a 1.6-km track, 5 d·wk^{-1}, during 24 wk. There were no significant changes in resting seated blood pressure in any of the walking groups. King et al. (25) recruited healthy, sedentary older men and women to determine the effectiveness of group- versus home-based exercise training of lower and higher intensities. Again, there were no significant training-induced changes in blood pressure within or between groups. Kingwell and Jennings (26) compared three levels of exercise intensity, that is, 50%, 60–70%, and 80–90% of maximal work load in normal men and women during a 4-wk program, but it should be noted that all other training characteristics differed among the groups. The authors concluded that the greatest blood pressure reduction was obtained with hard exercise; moderate exercise produced smaller reductions and short bursts of very hard exercise produced no changes at all. Braith et al. (4) studied healthy normotensive subjects 60–79 yr of age. Training at 70% of heart rate reserve and at 80–85% of heart rate reserve led to quite similar net reductions in blood pressure of approximately 8 mm Hg. Cox et al. (6) recruited healthy sedentary nonsmoking women aged 40–65 yr. Participants were randomly assigned to either a center-based or a home-based exercise program for an initial 6 months, whereafter both groups exercised at home for the next 6 months. Within each arm, subjects were further randomized to exercise at moderate intensity or at vigorous or hard

TABLE 2. Characteristics of the subjects and of the training programs in studies that randomized normotensive participants to different training regimens.

Study	Mean Age (range)	Gender	Design	Training Programs: Dur (wk)	Freq (per wk)	Time (min) (wu/ex/cd)	Intensity (%) Reported	Intensity (%) Adjusted	Methods
Different weekly frequency									
Gettman et al., 1996 (18)	24	M	PG	1. 20	1	30	85–90 (HRr)	—	W, R
	(20–35)			2. 20	3	30	85–90	—	W, R
				3. 20	5	30	85–90	—	W, R
				c. Nonendurance recreational activity group					
Jennings et al., 1986 (23)	22	M + F	CO	1. 4	3	5/30/5	60–70(WLm)	—	C
	(19–27)			2. 4	7	5/30/5	60–70	—	C
				c. Nonexercise control phase					
Different intensity with/without differences in time/frequency/methods									
Duncan et al., 1991 (11)	20–40	F	PG	1. 24	5	60	56 (HRm)	~30 (HRr)	Track-W
				2. 24	5	45	67	~47	Track-W
				3. 24	5	36	86	~78	Track-W
				c. Nonexercise control group					
King et al., 1991 (25)	50–65	M + F	PG	1. 52	5	30	60–73 (HRm)	~41 (HRr)	W, J, C (home)
				2. 52	3	40	73–88	~66	W, J, C (home)
				3. 52	3	40	73–88	~66	W, Tr-W, J, C (center)
				c. Nonexercise control group					
Kingwell and Jennings, 1993 (26)	37	M + F	CO	1. 4	5	60	50 (WLm)	—	W
	(22–59)			2. 4	3	30	65–70	—	C
				3. 4	5	15	80–90	—	C
				c. Nonexercise control phase					
Braith et al., 1994 (4)	66	M + F	PG	1. 26	3	45	70 (HRr)	—	W
	(60–79)			2. 26	3	35	80–85	—	Tr-W
				c. Nonexercise control group					
Cox et al. (6)	48	F	PG	1. 52	3	30	40–55 (HRr)	—	W + others
	(40–65)			2. 52	3	30	65–80	—	W + others

M, male; F, female; PG, parallel group; CO, crossover; Dur, duration; Freq, frequency; wu, warm-up; ex, exercise; cd, cool-down; HRr, heart rate reserve; WLm, maximal work load; HRm, maximal heart rate; W, walking; J, jogging; R, running; C, cycling; Tr, treadmill.

intensity, i.e., 40–55% or 65–80% of heart rate reserve, respectively. At 6 months, there was a significant fall in systolic, but not in diastolic blood pressure, with moderate-intensity, but not with vigorous-intensity exercise; the age- and weight-adjusted change in systolic blood pressure was estimated at 2.7 mm Hg ($P < 0.05$). This effect was no longer significant at 12 months. It is noteworthy that continuing participation in any regular exercise was a consistent predictor of the change in systolic blood pressure in this study.

TABLE 3. Characteristics of the subjects and of the training programs in studies that randomized hypertensive participants to different training regimens.

Study	Mean Age (range)	Gender	Design	Training Programs: Dur (wk)	Freq (per wk)	Time (min) (wu/ex/cd)	Intensity (%) Reported	Intensity (%) Adjusted	Methods
Different weekly frequency									
Nelson et al., 1986 (40)	44	M + F	CO	1. 4	3	5/35/5	60–70 (WLm)	—	C
	(25–62)			2. 4	7	5/35/5	60–70	—	C
				c. Nonexercise control phase					
Different intensity with/without differences in time/frequency/methods									
Hagberg et al., 1989 (19)	64	M + F	PG	1. 37	3	60	50 ($\dot{V}O_{2max}$)	~41 ($\dot{V}O_{2r}$)	W (home)
	(SD = 3)			2. 37	3	45–60	70–85	~73	W, Tr-W, J, C(sup)
				c. Nonexercise control group					
Matsusaki et al., 1992 (35)	47	M + F	PG	1. 10	3	5–10/60/5	50 ($\dot{V}O_{2max}$)	~40 ($\dot{V}O_{2r}$)	C
	(40–64)			2. 10	3	5–10/30–40/5	75	~65	C
Tashiro et al., 1993 (50)	46	M + F	CO + PG	1. 10	3	5–10/60/5	50 ($\dot{V}O_{2max}$)	~40 ($\dot{V}O_{2r}$)	C
	(33–57)			2. 10	3	5–10/30–40/5	75	~65	C
Marceau et al., 1993 (33)	43	M + F	CO	1. 10	3	5/45/10	50 ($\dot{V}O_{2max}$)	~44 ($\dot{V}O_{2r}$)	C
	(35–54)			2. 10	3	5/45/10	70	~67	C
				c. Nonexercise control phase					
Rogers et al., 1996 (45)	41	?	PG	1. 12	3	45	40–50 ($\dot{V}O_{2max}$)	~37 ($\dot{V}O_{2r}$)	Tr-W
	(SD = ~8)			2. 12	3	45	70–80	~71	Tr-W
				c. Nonexercise control group					
Moreira et al., 1999 (38)	50	M + F	PG	1. 10	3	5/30/5	20 (WLm)	~39 (HRr)[a]	C
	(SD = ~9)			2. 10	3	5/30/5	60	~70	C

M, male; F, female; PG, parallel group; CO, crossover; Dur, duration; Freq, frequency; wu, warm-up; ex, exercise; cd, cool-down; HRr, heart rate reserve; WLm, maximal work load; W, walking; J, jogging; C, cycling; Tr, treadmill; sup, supervised; $\dot{V}O_{2max}$, maximal oxygen uptake; $\dot{V}O_{2r}$, oxygen uptake reserve.
[a] Calculated from reported training heart rate.

TABLE 4. Results on blood pressure and physical work capacity in studies that randomized normotensive participants to different training regimens.

Study	Number			Systolic BP (mm Hg)		Diastolic BP (mm Hg)		
	Ne	Na		SED	Δ TR	SED	Δ TR	Δ PWC (%)
Gettman et al., 1976 (18)	24	11	CBP	1. 120	−3	77	−1	+11 ($\dot{V}O_{2max}$)
	26	20		2. 114	+3	76	+4	+13
	30	13		3. 120	0	73	+2	+17
	20	11		c. 118	−3	73	+4	−3
Jennings et al., 1986 (23)	12	12	SUP	1. 132	−10	69	−7	+11 ($\dot{V}O_{2max}$)
				2.	−12		−7	+24
			SIT	1. 111	−8	77	−5	+11
				2.	−10		−6	+24
Duncan et al., 1991 (11)	26	18	CBP	1. 108	−3	73	0	+4.4 ($\dot{V}O_{2max}$)
	26	12		2. 109	+1	74	−1	+9.3
	29	13		3. 105	0	70	0	+16
	21	10		c. 108	+2	74	+1	−5.8
King et al., 1991 (25)	197	45	CBP M	1. 115	−1	74	−2	+4.5 ($\dot{V}O_{2max}$)
	—	42		2. 117	−3	75	−2	+4.0
	—	40		3. 118	−3	75	−1	−5.9
	—	41		c. 119	−1	76	−2	−1.0
	160	29	F	1. 117	−6	73	−3	+4.0 ($\dot{V}O_{2max}$)
	—	35		2. 116	−3	73	−2	+6.1
	—	34		3. 119	−5	75	−2	+2.5
	—	34		c. 117	−3	72	−2	−3.8
Kingwell and Jennings, 1993 (26)	14	12	SUP	1. 123	−3	76	−2	+3 ($\dot{V}O_{2max}$)[a]
				2.	−5		−3	+3
				3.	0		−1	0
			ST	1. 120	−2	84	−1	+3
				2.	−4		−5	+3
				3.	−1		−2	0
Braith et al., 1994 (4)	19	19	CBP	1. 121	−9	72	−8	+17 ($\dot{V}O_{2max}$)
	14	14		2. 120	−8	75	−7	+25
	11	11		c. 121	+2	74	−1	0
Cox et al., 1996 (6)	126	53	CBP 6 mo	1. 111	−1.7	65	? (NS)	NS ($\dot{V}O_{2max}$)
	—	49		2.	+0.5		? (NS)	+6.9%
			12 mo	1. 111	+0.7	65	? (NS)	NS
				2.	+0.7		? (NS)	NS

Ne, number entered; Na, number analysed; M, male; F, female; CBP, conventional blood pressure; SUP, supine; SIT, sitting; ST, standing; BP, blood pressure; SED, sedentary; TR, training; NS, not significant; PWC, physical work capacity; $\dot{V}O_{2max}$, maximal oxygen uptake.
[a] Versus nonexercise sedentary control phase, when $\dot{V}O_{2max}$ was 17% above baseline values.

Hagberg et al. (19) were the first to compare the blood pressure response to moderate- and hard-intensity exercise training, i.e., training at 50% and 77% of maximal oxygen uptake, respectively, in older hypertensives. It should be noted that the moderate-intensity program consisted of walking at home, whereas the other group performed a variety of supervised exercises. The authors reported that the blood pressure reduction was more pronounced after moderate-intensity training, but this was not the case for the blood pressure measured during the hemodynamic assessment testing session. Moreover, blood pressure during fixed submaximal exercise was reduced after training in the hard-intensity group but not in the moderate-intensity group. Matsusaki et al. (35) and Tashiro et al. (50) compared exercise at two workloads in patients with mild hypertension. The lower workload corresponded to the workload at the first lactate breaking point, i.e., approximately 50% of maximal oxygen uptake, and the subjects in the higher workload group exercised at the load corresponding to 4 $mmol \cdot L^{-1}$ of blood lactate, which was approximately 75% of maximal oxygen uptake. Whereas Matsusaki et al. (35) found that the reduction in systolic but not diastolic blood pressure was greater at lower intensity exercise, Tashiro et al. (50) observed a slightly better response of diastolic but not of systolic pressure in the higher work-load group. Marceau et al. (33) evaluated previously sedentary subjects with mild to moderate hypertension in a crossover fashion after a sedentary control period and after training at moderate and hard intensity corresponding to 50% and 70% of maximal oxygen uptake, respectively. Blood pressures measured at supine rest and during submaximal exercise were not significantly influenced by training, whereas both training intensities reduced average 24-h blood pressure by about 5 mm Hg; however, the lower intensity training reduced daytime blood pressure and the higher intensity training only nighttime pressure. Rogers et al. (45) compared the effects of training at about 45% and at about 75% of maximal oxygen uptake in patients with borderline hypertension and found that the lower intensity exercise was more effective than the higher intensity exercise in reducing resting blood pressure and, in addition, the blood pressure responses to stress. Finally, Moreira et al. (38) randomized hypertensive patients to two different levels of aerobic physical training, i.e., 20% or 60% of their maximal work load on a cycle ergometer. However, from the reported heart rate during exercise training, it can be calculated that training intensity corresponded to approximately 39% and 70% of heart rate reserve, respectively. The results on conventional blood pressure and on 24-h ambulatory blood pressure were slightly more pronounced in the higher intensity group, but the differences were not significant.

Evidence statement. There is no convincing evidence that the blood pressure response to dynamic aerobic training differs according to training intensity when between 40%

TABLE 5. Results on blood pressure and physical work capacity in studies that randomized hypertensive participants to different training regimens.

Study	Number			Systolic BP (mm Hg)		Diastolic BP (mm Hg)		
	Ne	Na		SED	Δ TR	SED	Δ TR	Δ PWC (%)
Nelson et al., 1986 (40)	17	13	SUP	1. 143	−11	96	−9	+17 ($\dot{V}O_{2max}$)
				2.	−16		−11	+19
			ST	1. 147	−12	101	−11	+17
				2.	−14		−13	+19
Hagberg et al., 1989 (19)	14	11	CBP	1. 164	−22	94	−12	+10 ($\dot{V}O_{2max}$)
	10?	10?		2. 157	−10	99	−11	+28
	9?	9?		c. 154	−2	90	−2	+5
			HEM	1. 158	−7	90	−3	+10
				2. 160	−6	100	−9	+28
				c. 152	−1	90	−1	+5
Matsusaki et al., 1992 (35)	16	16	CBP	1. 152	−9	96	−6	+29 (WLlt)
	14	10		2. 153	−3	99	−5	+56
Tashiro et al., 1993 (50)	10	8	CBP	1. 154	−6	93	−4	+35 (WLlt)
				2. 149	−7	96	−9	+24
Marceau et al., 1993 (33)	11	9	CBP	1. 130	+2	87	+3	+2.9 ($\dot{V}O_{2max}$)
				2.	−2		0	+14
			24-h	1. 145	−4	91	−3	+2.9
				2.	−3		−3	+14
Rogers et al., 1996 (45)	8	6	CBP	1. 140	−15	93	−6	+3.7 ($\dot{V}O_{2max}$)
	9	7		2. 138	−4	91	−1	+28
	6	5		c. 140	−1	93	−3	−1.1
Moreira et al., 1999 (38)	14	14	CBP	1. 156	−9	98	−7	(Δ WLm
	14	14		2. 153	−15	97	−8	similar in two
			24-h	1. 137	−2	92	−3	groups)
				2. 144	−6	93	−3	

Ne, number entered; Na, number analyzed; CBP, conventional blood pressure; HEM, hemodynamic measurements; SUP, supine; SIT, sitting; ST, standing; BP, blood pressure; SED, sedentary; TR, training; PWC, physical work capacity; $\dot{V}O_{2max}$, maximal oxygen uptake; WLm, maximal work load; WLlt, work load at lactate threshold.

and 70% of net maximal exercise performance (moderate to hard intensity). There are insufficient data on the effects of light and very hard exercise. Evidence Category A.

Evidence statement. The blood pressure response to dynamic aerobic training appears to be similar for frequencies between three and five sessions per week and for session times between 30 and 60 min. There are few data on other exercise regimens except that seven sessions per week may elicit a slightly greater blood pressure response than three sessions per week. Evidence Category B.

Influence of Volume of Physical Activity

Net energy expenditure (kilocalories per week) resulting from the training programs was calculated according to the following formula: (baseline peak $\dot{V}O_2$ ($mL \cdot min^{-1} \cdot kg^{-1}$) − 3.5) × 0.005 ($kcal \cdot mL^{-1}$ $\dot{V}O_2$) × body mass (kg) × net training intensity (%) × training frequency ($n \cdot wk^{-1}$) × time per session (min).

Data were available in 57 of the 68 study groups, 30 from single program randomized controlled studies and 27 from studies in which subjects were randomized to different training regimens and that included a control group or period. Net extra energy expenditure ranged from 363 to 1866 $kcal \cdot wk^{-1}$ (median, 850 $kcal \cdot wk^{-1}$). Overall, there were no significant relationships between the net changes of systolic blood pressure ($y = -5.66 + 0.0021 * x$; $r = 0.14$; $P = 0.20$) and of diastolic blood pressure ($y = -2.34 - 0.0002 * x$; $r = -0.02$; $P = 0.86$) with the net weekly energy expenditure.

DISCUSSION

There is good evidence from randomized controlled trials that dynamic physical training reduces blood pressure (13,16,20). In our recent meta-analysis of such trials of at least 4-wk duration (13), we concluded that the blood pressure lowering effect is small but significant in normotensive subjects, averaging approximately 3/2 mm Hg after adjustment for control data, and that the net effect is more pronounced in hypertensives who benefit from an average blood pressure reduction of 7/6 mm Hg. Net training intensity was reported or could be calculated in most of these studies and averaged approximately 65% of maximal work load, heart rate reserve, or oxygen uptake reserve. Our cross-sectional analysis of studies in which only one training intensity was applied in one or more training groups or phases revealed that divergent blood pressure responses between study groups could not be explained by training intensity, which ranged from 43–87% (Figs. 1 and 2). Also, other characteristics of the training regimens, i.e., weekly frequency and time per session, were not related to the blood pressure response; it should be noted, however, that the training programs were designed to elicit an increase in exercise performance and that the ranges of these training characteristics were small. When frequency, time per session, and exercise intensity were combined in multivariable regression analysis, they explained less than 5% of the variance of the blood pressure response. The slightly lesser reduction of systolic pressure with longer duration of training, which could last up to 1 yr, may be explained by decreased adherence as shown by Cox et al. (6).

Several authors addressed the dose-response question by randomizing participants to training programs involving different training frequencies. Whereas Gettman et al. (18) found no differences in blood pressure response between training one, three, and five times per week, Jennings et al. (23) and Nelson et al. (40) observed slightly greater blood pressure falls at a frequency of seven times per week than at

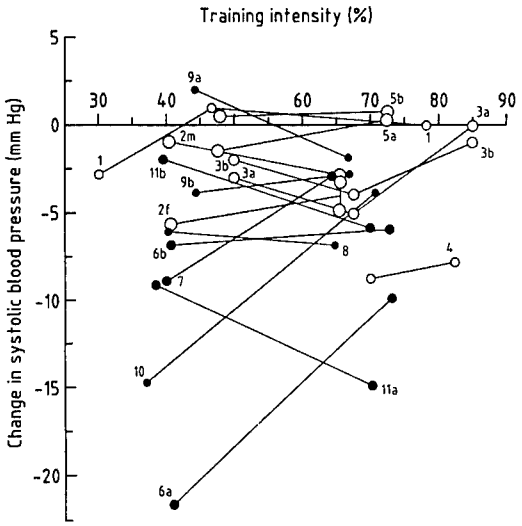


FIGURE 3—Changes in systolic blood pressure with training versus exercise intensity in studies in which two or more intensities have been compared, either in normotensive (*open circles*) or in hypertensive subjects (*closed circles*). The sizes of the circles correspond to the number of analyzable subjects. Training intensity is expressed as percent of maximal work load, heart rate reserve, or oxygen uptake reserve. The numbers in the figure correspond to the following references: 1, Duncan et al. (11); 2, King et al. (25) (m = male; f = female); 3, Kingwell and Jennings (26) (a, supine BP; b, standing BP); 4, Braith et al. (4); 5, Cox et al. (6) (a, 6 months; b, 12 months); 6, Hagberg et al. (19) (a, conventional BP; b, BP during hemodynamic study); 7, Matsusaki et al. (35); 8, Tashiro et al. (50); 9, Marceau et al. (33) (a, conventional BP; b, average 24-h BP); 10, Rogers et al. (45); and 11, Moreira et al. (38) (a, conventional BP; b, average 24-h BP).

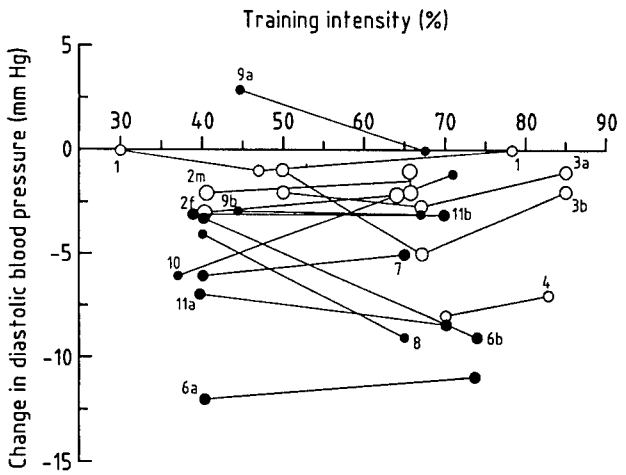


FIGURE 4—Changes in diastolic blood pressure with training versus exercise intensity in studies in which two or more intensities have been compared, either in normotensive (*open circles*) or in hypertensive subjects (*closed circles*). The sizes of the circles correspond to the number of analyzable subjects. Training intensity is expressed as percent of maximal work load, heart rate reserve, or oxygen uptake reserve. The numbers in the figure correspond to the following references: 1, Duncan et al. (11); 2, King et al. (25) (m = male; f = female); 3, Kingwell and Jennings (26) (a, supine BP; b, standing BP); 4, Braith et al. (4); 5, Cox et al. (6) (a, 6 months; b, 12 months); 6, Hagberg et al. (19) (a, conventional BP; b, BP during hemodynamic study); 7, Matsusaki et al. (35); 8, Tashiro et al. (50); 9, Marceau et al. (33) (a, conventional BP; b, average 24-h BP); 10, Rogers et al. (45); and 11, Moreira et al. (38) (a, conventional BP; b, average 24-h BP).

three times per week. Others compared different training intensities. Changes in blood pressure were small to nonexistent in normotensive subjects and there was no consistent evidence that a net intensity of around 70% would lead to different results in comparison with an intensity of 30–50% (6,11,25,26). Kingwell and Jennings (26) suggested that training at 80–90% of maximal work load was less effective than training at 65–70%, but Braith et al. (4) observed similar net blood pressure reduction of about 8 mm Hg when training at 70% and at 80–85% of heart rate reserve. The results were more variable in hypertensives. Three studies (19,35,45) found a lesser reduction of systolic blood pressure after training at exercise intensities between 65% and 75% of oxygen uptake reserve than at about 40%. These results were not observed for diastolic blood pressure, except in one study (45). It should furthermore be noted that in one study (19) the higher training intensity led to similar or even greater reductions in systolic pressure than did the lighter exercise when pressure was measured in other circumstances, that is, during the hemodynamic measurements and on exercise testing, respectively. The results of Matsusaki et al. (35) were not confirmed in another study of the same group, in which the same training regimen was applied (50). Marceau et al. (33) found no significant effects of moderate and hard exercise on supine, sitting, and exercise blood pressure, but 24-h ambulatory blood pressure was equally reduced by about 5 mm Hg. The unexpected finding that moderate exercise reduced daytime blood pressure and hard exercise nighttime pressure needs confirmation. Only Moreira et al. (38) attempted to compare moderate to hard exercise (60% of maximal work load) with light exercise (20% of maximal work load). However, recalculation of exercise intensities from the reported heart rates indicates that participants have been training at about 70% and 40% of heart rate reserve, respectively. The response of particularly systolic blood pressure tended to be greater with hard exercise, but the between-group differences were not significant. In agreement with previous data (52), the ambulatory blood pressure response was confined to daytime pressure. It should also be considered that the training programs of several of these studies did not only differ in intensity, as shown in Tables 2 and 3. The duration of the training sessions was often shorter in the high-intensity programs. The lighter exercise programs could be home-based and unsupervised, whereas the higher intensity exercises were usually supervised and performed in a specialized center. Finally, the type of exercises could differ among the groups.

The question was addressed whether the blood pressure response was related to the volume of physical activity or the net extra weekly energy expenditure associated with the various training programs. We have not found such relationships in the 57 training groups or programs in which energy expenditure could be calculated from the available data. Such a far-reaching analysis should, however, be interpreted with great caution.

Two further studies may be of interest. Dunn et al. (12) compared a lifestyle physical activity counseling intervention with a traditional gymnasium-based structured exercise intervention at 50–85% of maximal aerobic power in

healthy sedentary, middle-aged men and women. Changes in blood pressure were similar after 6 months. However, training intensity was not reported in the lifestyle group, and it cannot be excluded that the results were influenced by the application of cognitive and behavioral strategies. Young et al. (57) randomized sedentary older adults to a 12-wk moderate-intensity aerobic exercise program at 40–60% of heart rate reserve and a T'ai Chi program of light activity. Both programs led to small and similar reductions in blood pressure compared with preexercise control data. Absence of control groups, however, precludes judgment of the net effect on blood pressure of these programs.

In conclusion, training from three to five times per week during 30–60 min per session reduces blood pressure, particularly in hypertensives. There is some evidence that exercising seven times per week would be slightly more effective than three sessions per week. Training at about 40–50% of net maximal exercise performance (moderate exercise) does not appear to be less effective than training at about 70% (hard exercise) with regard to blood pressure reduction. The suggestion that hard-intensity training would be less effective than training at lower intensity cannot be definitely accepted. Insufficient data are available on exercise intensities of less than about 40%, that is, light and very light exercise, and of more than 84%, or very hard exercise.

Research Priorities

We have previously pointed out that several important scientific criteria have not always been observed in studies that assessed the influence of physical training on blood pressure, such as regular follow-up of control subjects, attention to other lifestyle factors, adequacy of the statistical analyses, and blinded or automated blood pressure measurements. Furthermore, the mechanisms of the training-induced blood pressure changes remain largely unknown (13). Such remarks also apply to studies in which different training regimens have been compared. Furthermore, uncertainty remains whether hard- and particularly very hard-intensity training would be less effective than moderate-intensity training with regard to blood pressure control. However, this question may be of scientific interest but has little practical value for the exercise physiologist or the clinician because he or she will be happy to prescribe moderate rather than hard exercise, particularly in the hypertensive patient. There is a lack of controlled data on the blood pressure response to exercise intensities below approximately 40% of net maximal exercise performance. Finally, when one aims to investigate the effect of variations in a particular exercise characteristic on the blood pressure response, care should be taken to keep the remaining characteristics of the training program as constant as possible.

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Chair summary and comments

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Since time immemorial, physicians have believed in the value of physical activity for good health. But until this century, most evidence to support this position has been empirical and anecdotal. Only since World War II have quantitative data been collected either from observations in occupational settings or from studies of those engaged in personal chores or participating in leisure-time behaviors. These data provided the evidence that upholds physical activity for health. Dose-response issues, i.e., physical activity for health, have helped satisfy canons of causality (statistical association, temporal sequence, consistency, persistence, independence, dose-response relation, etc.) (4,5,8) and will help establish recommendations of exercise for the public's health.

Walking, stair climbing, recreational activities, and sports play (separately and in combination) lower risk of specific disease occurrence. Physical activity not only prevents certain diseases in a dose-response relation, it can be used effectively to treat such conditions. The question is not merely whether a physically active and physiologically fit way of life prevents disease and extends longevity. The question now is what kinds, how much, how intense, and for whom should physical activity be prescribed for optimal health?

FINDINGS

Haskell states that various doses of exercise deserve attention when considering the priority of health outcomes, interindividual variations in outcomes, and the relation of health benefits to health risks. Concern is directed at whether a higher intensity or a greater volume of endurance-type exercise is preferable in producing health benefits, and whether benefits derived from accumulation of short bouts of exercise performed frequently are as valuable as longer bouts performed infrequently (3).

In Lee and Skerrett's review of worldwide publications, evidence of an inverse linear dose-response relation between volume of physical activity and rates of all-cause mortality has become clear. This relation holds for men and women, and for younger and older individuals. Energy expenditure of 1000 kcal·wk^{-1} is associated with a significant reduction in risk of death; further reductions in risk are observed at higher volumes of exercise; but there are only limited data suggesting that less than 1000 kcal·wk^{-1} is associated with lower risk. Dose-response data leave us uncertain as to whether vigorous-intensity activity confers additional benefit beyond its contribution to volume of physical activity when compared with moderate-intensity activity (7).

Kohl's analyses of the same publications cited in the previous paragraph indicate that cardiovascular disease incidence (fatal and nonfatal), and specifically ischemic heart disease, is related to physical activity in an inverse, dose-response fashion. It is uncertain, however, as to what dose should be accumulated, i.e., by mode, volume, intensity, frequency, duration, and by various interactions with other characteristics. Also, accumulation of a total dose of low-intensity physical activity over an extended period has not provided any protection against cardiovascular disease. High volume of activity shows only weak evidence for protection against stroke (6).

Fagard reviewed randomized intervention trials of different training intensities on blood pressure response. The overall net changes in blood pressure averaged −3.4/−2.4 mm Hg. Baseline blood pressure was an important determinant of blood pressure responses: response in normotensives was −2.6/−2.7 mm Hg; in hypertensives, −2.4/−5.8 mm Hg. Peak oxygen uptake increased by 11%, heart rate decreased by 7%, and BMI decreased by only 1%. Training intensities and frequencies had little effect, but duration of the training effect favorably influenced systolic and not diastolic pressure. Many other dose-response data are presented (2).

FUTURES

Through epidemiological observations, we have come to know that physical activity protects against several diseases and delays death. Along the way, physical activity improves functional capacity; enhances mood, thought, and psychological behavior; and postpones the infirmities and disabilities of old age.

To clarify and extend these issues, we need methodological advances in physical activity assessment; additional observations on changes in physical activity as they relate to health outcomes; analyses of relative versus absolute intensities in affecting disease risk; additional

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observations among women and ethnically diverse populations; more attention on bias, chance, and potential confounders; and collaborative reanalyses of many studies on a common basis (1). Some weak associations that are socially important may be detected only by epidemiological investigation. Dose-response relations of physical activity as cause, and health benefits as effect, will lead to exercise prescriptions and intervention techniques that will advance the public's health.

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Effects of exercise on glucose homeostasis in Type 2 diabetes mellitus

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ABSTRACT

KELLEY, D. E., and B. H. GOODPASTER. Effects of exercise on glucose homeostasis in Type 2 diabetes mellitus. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., pp. S495–S501. **Purpose:** This review has evaluated the effectiveness of physical activity in the treatment and prevention of Type 2 diabetes mellitus (DM). **Methods:** The available literature was reviewed through a computerized search (MEDLINE, 1966–2000) to classify studies examining the influence of physical activity on the treatment and prevention of Type 2 DM. Additional studies were reviewed through ancestral searches from their bibliographies. **Results:** It is not possible at the present time to discern from the available literature whether a dose-response relationship exists between exercise volume or intensity and improvements in glucose control in Type 2 DM. Large-scale, prospective studies indicate that higher levels of physical activity are clearly associated with a lower incidence of Type 2 DM. However, no randomized controlled trials have been conducted to address the dose-response effect of exercise or physical activity on diabetes treatment or prevention. **Conclusion:** It is uncertain whether there is a dose-response effect of exercise on improved glucose control in Type 2 DM. There does appear to be, however, a limited amount of evidence suggesting that increasing levels of physical activity contribute to better diabetes prevention. Clearly, additional studies are needed to determine the influence of physical activity on the treatment and prevention of Type 2 DM. **Key Words:** PHYSICAL ACTIVITY, EXERCISE, TYPE 2 DIABETES MELLITUS, BLOOD GLUCOSE

Type 2 diabetes mellitus (DM) is a serious metabolic disorder. The incidence and prevalence of Type 2 DM continue to increase in much of the world, related in part to the increasing prevalence of obesity and sedentary lifestyles, as well as to the aging of the population in most westernized countries. The pathophysiology of Type 2 DM involves impaired insulin secretion, and impaired insulin action in regulating glucose and fatty acid metabolism in the liver, skeletal muscle, and adipose tissue. Many individuals with Type 2 DM have hypertension and perturbations of lipoprotein metabolism, as well as other manifestations of the insulin resistant syndrome, such as altered fibrinolysis. In addition to the risk for development of diabetes-specific complications of retinopathy, diabetic nephropathy and diabetic neuropathies, Type 2 DM is recognized as a substantial risk factor for cardiovascular disease.

It has been traditional in discussions of the therapy of Type 2 DM to place emphasis on the positive value of exercise. The purpose of this review is to examine data from randomized clinical trials, as well as other peer-reviewed research reports, to critically assess the therapeutic value of exercise in the management of Type 2 DM. The first and major area of consideration will be to review data on the effect of exercise on glucose homeostasis in individuals with an established diagnosis of Type 2 DM. Two related topics are to examine the effect of exercise on lipids and blood pressure in Type 2 DM. This review will also examine data regarding the effectiveness of exercise in the prevention of Type 2 DM and in the prevention of mortality from Type 2 DM. When possible, this report will attempt to assess whether a dose-response relationship between volume or intensity of exercise and outcomes can be discerned in relation to Type 2 DM.

CURRENT STATUS OF KNOWLEDGE

Effects of exercise on hyperglycemia in patients with type 2 DM (Evidence Category B). The positive impact of exercise to improve glucose control in Type 2 DM is widely endorsed in the literature and in clinical teaching. The findings from a number of relatively large clinical trials of the effect of aerobic exercise on glucose homeostasis in individuals with Type 2 DM are shown in Table 1 (2,21,23,31,32,35–37,39). There are also a number of excellent prior review articles from the past two decades that have addressed this topic (10,15,18–20) and that have, in turn, examined a number of earlier intervention trials; these useful resources were examined in preparing this report. An effect of exercise to improve glucose control can be found in most, but certainly not all of these clinical trials. Moreover, there are several important caveats to consider in the assessment of whether physical activity produces an improvement in glucose control in patients with Type 2 DM.

First, the magnitude of the improvement in glucose control that can be attributed to the exercise intervention is generally modest. If an effect on HbA1c is obtained, the

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TABLE 1. Effects of aerobic exercise on glucose homeostasis in Type 2 DM.

Study	Study Design	Subjects	ExerciseFrequency/ Intensity/Duration	Intervention Duration	Glucose Control	Insulin Sensitivity	Insulin Secretion
Ronnemaa et al., 1986 (36)	RCT: exercise	25 men and women	5–7×/wk; 70% $\dot{V}O_{2max}$; 45 min	4 mo	HbA1c ↓ 1%; FPG ↓ 2-h PPG ↓	NC	Fasting insulin ↓ 2-h PPI ↓
Uusitupa, 1996 (39)	RCT: diet + exercise	86 men and women	3–4×/wk; aerobic; 30–60	12 mo	HbA1c ↓ 0.5%; NC HbA1c in 50%; FPG ↓	NC	Fasting insulin ↓
Leon et al., 1984 (23)	RCT: 5 types of exercise intervention	50 men	2–4×/wk; 70% $\dot{V}O_{2max}$; 30–60 min	3 mo	FPG NC HbA1c NC 2-h PPG ↓ 60 min ex	NC	Fasting insulin ↓ PPI ↓
Krotkiewski et al., 1985 (21)	Nonrandomized	24 men and women	3×/wk; 80% $\dot{V}O_{2max}$; 50 min	3 mo	FPG NC 2-h PPG ↓	↑	Fasting insulin ↓ PPI ↓
Bogardus et al., 1984 (2)	RCT: diet + exercise vs diet only	18 men and women	3×/wk; 75% $\dot{V}O_{2max}$; 30 min	3 mo	FPG: no additional effect of exercise	↑	IVGT-Exercise ↓ vs diet only
Poirier et al., 1996 (31)	Nonrandomized	11 men	3×/wk; 60% $\dot{V}O_{2max}$; 60 min	6 mo	FPG NC HbA1c NC	NC	Fasting insulin ↓
Reitmann et al., 1984 (32)	Nonrandomized	6 men and women	5–6×/wk; 75% $\dot{V}O_{2max}$; 20–40 min	1.5–2.5 mo	FPG ↓ PPG ↓ HbA1c NC	NC HGP ↓	Fasting insulin ↓ PPI ↑
Schneider et al., 1992 (36)	NRCT	111 men and women	3–4×/wk; 65–75% HRR; 40–60 min	3 mo	FPG ↓		
Segal et al., 1991 (37)	Nonrandomized	6 men	4×/wk; 70% $\dot{V}O_{2max}$; 70 min	3 mo	FPG NC PPG NC	NC HGP ↓	Fasting insulin NC PPI NC

RCT, randomized controlled trial; NRCT, nonrandomized controlled trial; NC, no change; $\dot{V}O_{2max}$, maximal oxygen uptake; FPG, fasting plasma glucose; PPG, postprandial glucose; PPI, postprandial insulin; HHR, heart rate reserve (maximal HR–resting HR).

decrease is generally of 0.5 to 1.0%, which in the context of therapeutic efficacy would be considered modest. This amount of improvement in HbA1c is just at the threshold that many regulatory agencies (e.g., FDA) regard as the minimum criteria for approval of new pharmacological agents for the lowering of hyperglycemia in Type 2 DM. Moreover, in about one third of the reviewed studies, no change in HbA1c was found in response to exercise, even though an improvement in fitness was reported in these trials. A similar pattern is noted with respect to the effect of exercise on fasting plasma glucose. Given the fairly modest responses in glucose control, and indeed variable responses despite exercise interventions that appear to have been effective in achieving improved fitness, it is not possible at the present time to discern whether a dose-response relationship exists between exercise volume or intensity and improvements in glucose control in Type 2 DM.

A second caveat in evaluating the effect of exercise on glucose homeostasis is that it is relatively difficult to dissociate the effects of exercise from the effects of dietary interventions. Many trials incorporate nutritional interventions, including weight reduction interventions in conjunction with exercise interventions. In clinical practice, patients with Type 2 DM are commonly given instructions in lifestyle interventions that combine nutrition and exercise, so it is somewhat artificial to attempt to segregate the two. However, for the purpose of this review on the effectiveness of exercise, it must be recognized that even studies purporting to primarily examine the impact of exercise intervention generally include some type of nutritional intervention. Often, this intervention is directed at weight loss for the overweight or obese patient with Type 2 DM. In a few studies that deliberately intervened (by carefully increasing calorie intake to offset the expenditure during exercise) to prevent weight loss, exercise was observed to have only nominal or no effect on glucose control in Type 2 DM.

A third caveat is that in some studies any impact of exercise to improve glucose control is muted because doses of glucose-lowering medications were adjusted. In other words, although no clear effect on glucose control was observed in comparing exercise versus control groups, it is reported that the doses of diabetic medications were reduced in the exercise group. Although this might indicate a "positive" impact of exercise, these data must be regarded as of only marginal significance. The criteria used for adjusting medication is rarely provided, the amount of reduction appears modest and to have occurred in less that half of the subjects, and whether the reductions were done to respond to lack of need for medication or to compensate for adverse effects of medication during exercise (e.g., hypoglycemia) is not defined.

There were three potential areas where exercise does appear to have positive effects, although these data are not established in a highly robust manner and usually are derived from relatively small studies without control (nonexercise) groups. First, exercise appears to improve (decrease) the insulin resistance of peripheral tissues, and more specifically, to alleviate the defect of insulin-stimulated glycogen metabolism in skeletal muscle. This finding derives more from the review of a number of relatively small but informative physiological studies (5,14,17,30,33). To some extent, this finding is complicated by considerations of whether the effect on insulin sensitivity is related to an actual "training effect" or is the short-term effect of the most

recent exercise session. Second, exercise was found to improve postprandial hyperglycemia, even if the effect on fasting hyperglycemia was minor. There are some data that suggest there is improvement of postprandial insulin secretion. This is an area that warrants more careful scrutiny, since it would be a relatively unique positive impact in that neither weight loss *per se* nor most classes of oral pharmacological agents have been shown to specifically improve early phases of postprandial insulin secretion. Third, a relatively small number of studies suggest that exercise acutely lowers hepatic glucose production in Type 2 DM (17,27). Fourth, studies of patterns of substrate utilization during exercise appear to indicate that there is substantial similarity in the metabolism of glucose by peripheral tissues in comparing nondiabetic and Type 2 DM individuals, at least at moderate intensity exercise (4,9). This last point would indicate that despite marked defects in insulin-stimulated glucose metabolism in peripheral tissues (mainly skeletal muscle), contraction-mediated patterns of substrate use are substantially similar in diabetic and nondiabetic individuals.

A smaller number of studies have examined the impact of exercise on blood pressure and lipoprotein metabolism specifically in relation to Type 2 DM (2,21–23,31,34–36,39). These data are summarized in Table 2. The data on effect on blood pressure are equivocal, with some studies demonstrating modest lowering of blood pressure and other studies reporting no changes. Most, though not all studies indicate that aerobic exercise increases high-density lipoprotein (HDL)-cholesterol, and some studies also report lowering of low-density lipoprotein (LDL)-cholesterol; generally, those studies that do find these changes report the changes are of approximately 10% difference from baseline. A few studies report lowering of plasma triglyceride, but this is inconsistent. As with the data on glucose metabolism, the interpretation of an effect of exercise *per se* is complicated by concomitant nutritional interventions. It is not possible to establish whether a dose-response relationship exists within the responses of blood pressure and lipoproteins to exercise in Type 2 DM.

The large majority of clinical trials that have examined exercise effects on glucose control and other aspects of metabolism in Type 2 DM have examined the effect of aerobic exercise, usually treadmill walking, jogging, or cycling. However, a few studies have tried to examine the effects of resistance training and whether this is similar to the effects of aerobic exercise. The results of these trials are shown in Table 3 (7,12,38). To summarize these data, the impact of several months of resistance training is an improvement in strength with modest to little effect on glucose control, lipids, or insulin.

Evidence statement: chronic physical activity prevents or delays the development of Type 2 DM (Evidence Category B). There is strong epidemiological evidence that physical activity is related to the incidence of Type 2 DM. Both cross-sectional and retrospective studies have clearly demonstrated associations between physical activity and Type 2 DM, but it is difficult to establish causality from these data. Moreover, these studies typically have not attempted to determine a dose-response effect of exercise intensity or duration on the incidence or development of diabetes. Prospective epidemiological studies do, however, contain limited evidence that a dose-response effect does exists for the association between physical activity and the incidence of Type 2 DM (as shown in Fig. 1). These studies are more powerful than other observational studies, because they identify subjects who are initially free from diabetes, although they may be at higher risk. It is from these recent population-based studies in which we can infer much of the protective effect of physical activity in the prevention of Type 2 DM. A summary of these studies is shown in Table 4.

Manson and colleagues have conducted three prospective studies on the association between physical activity and the development of diabetes (13,25,26). In the first study (26),

TABLE 2. Effects of aerobic exercise on lipids and BP in Type 2 DM.

Study	Study Design	Subjects	Exercise Frequency/ Intensity/Duration	Study Duration	Blood Lipids	Heart Rate Blood Pressure
Ronnemaa et al., 1988 (36)	RCT	25 men and women	5–7×/wk; 70% $\dot{V}O_{2max}$; 45 min	4 mo	LDL-C ↓ HDL-C ↑ Triglycerides NC	
Uusitupa et al., 1996 (39)	RTC: diet + exercise, control	86 men and women	3–4×/wk; aerobic; 30–60 min	12 mo	LDL-C ↓ HDL-C ↑ Triglycerides ↓	
Leon et al., 1984 (23)	RTC: 5 types of exercise	50 men	2–4×/wk; 70% $\dot{V}O_{2max}$; 30–60 min	3 mo		Resting HR NC Resting BP NC
Krotkiewski et al., 1985 (21)	Nonrandomized	24 men and women	3×/wk; 80% $\dot{V}O_{2max}$; 50 min	3 mo		Exercise HR ↓ Resting BP NC
Poirier et al., 1996 (31)	Nonrandomized	11 men	3×/wk; 60% $\dot{V}O_{2max}$; 60 min	6 mo	LDL-C NC HDL-C NC Triglycerides NC	
Lehman et al., 1995 (22)	RCT	27 men and women	3×/wk; 60% $\dot{V}O_{2max}$; 40 min	3 mo	LDL-C NC HDL-C ↑ Triglycerides ↓	Exercise HR ↓ Resting BP ↓

RCT, randomized controlled trial; $\dot{V}O_{2max}$, maximal oxygen uptake; NC, no change; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HR, heart rate; BP, blood pressure.

TABLE 3. Effects of resistance training exercise on glucose control in Type 2 DM.

Study	Study Design	Subjects	Exercise	Study Duration	Glucose Control	Insulin Sensitivity	Insulin Secretion
Eriksson et al., 1998 (7)	RCT	14 men and women IGT; no diabetes	3×/wk 1 h Circuit training	3 mo	NC	NC	NC
Smutok et al., 1994 (38)	RCT	8 Type 2 DM 16 IGT men and women	Resistance vs aerobic training	5 mo	PPG ↓		Fasting insulin ↓ PPI NC
Honkola et al., 1997 (12)	RCT	37 men and women	2×/wk Circuit training	5 mo	HbA1c ↓ by 0.5%		

RCT, randomized controlled trial; IGT, impaired glucose tolerance; NC, no change; PPG, postprandial glucose; PPI, postprandial insulin.

the frequency of "vigorous" exercise was related to a decreased incidence of diabetes in a cohort of 87,252 women over an 8-yr period. When adjusted for age and body mass index (BMI), women who engaged in regular vigorous exercise reduced their relative risk for the development of diabetes. However, a clear dose-response effect of physical activity in the prevention of diabetes in these women was not observed. The intensity of exercise defined by questionnaire as "vigorous" was determined by the question, "At least once a week, do you engage in any regular activity similar to brisk walking, jogging, bicycling, etc., long enough to work up a sweat?" Results from a subsequent study conducted by the same author (25) in 21,271 men mirrored these results, indicating that participation in vigorous exercise was associated with a decreased relative risk for the development of diabetes. In addition, vigorous exercise performed five or more times per week reduced the relative risk to 0.58 compared with 0.77 for vigorous exercise performed one time per week. In a more recent prospective analysis from the Nurses Health Study, these investigators found that, in addition to participation in vigorous physical activities, higher physical activity attributable to walking was also associated with a reduced relative risk for diabetes (13). Thus, results from these studies indicate the presence of a dose-response effect of physical activity in the prevention of Type 2 DM.

Helmrich et al. (11) found a 6% decrease in the age-adjusted risk for the development of diabetes for each 500-kcal increase in weekly leisure time physical activity energy expenditure. This observed protective effect of exercise on diabetes prevention was greater in obese individuals. In another study (24), a group of 897 middle-age Swedish men who participated in at least 40 min·wk^{-1} at an intensity of at least 5.5. METs had a reduced risk for the development of diabetes after adjusting for age, baseline glucose values, BMI, serum triglyceride levels, parental history of diabetes, and alcohol consumption. Moreover, the obese men in this study who exercised at least this duration and intensity reduced their risk for developing diabetes by 64% compared with those who did not exercise to this level. Although these results on the whole do not indicate a threshold effect for the prevention of diabetes by increased physical activity, they do suggest at least some degree of a dose-response relationship.

In another recent prospective study, Wannamethee et al. (40) found that physical activity was associated with a decreased prevalence of diabetes in men who were mostly white. Unlike many of the earlier large-scale prospective studies, this study specifically examined the dose-response effect of increased physical activity, and it was found that there was a deceased incidence of diabetes with increasing levels of physical activity ranging from regular walking and cycling to recreational to sporting or vigorous. After adjusting for age and BMI, a clear dose-response effect persisted for physical activity and a reduced relative risk for the development of diabetes. Of note, there was also a decreased risk of hyperinsulinemia and hyperlipidemia, and that these markers of the insulin resistance syndrome were also influenced by physical activity in a dose-response manner.

The apparent benefits of regular physical activity have also been extended to other ethnic groups (1,3,6,16,28). James et al. examined the role of physical activity in incidence of diabetes

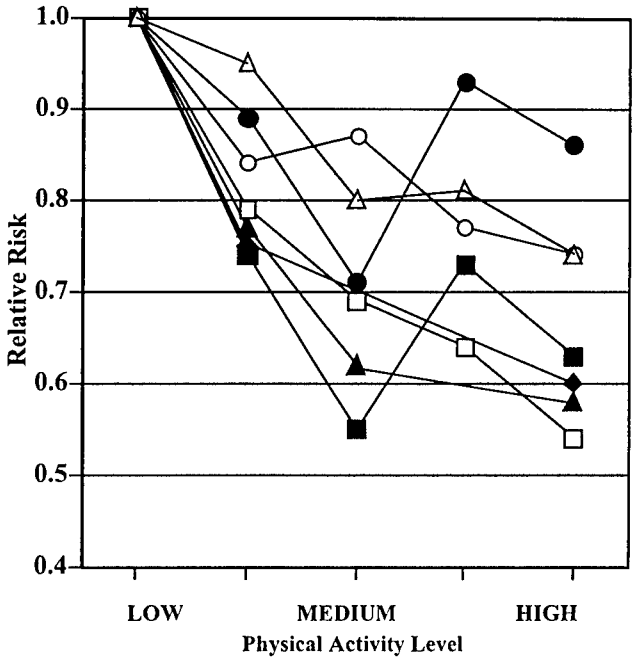


FIGURE 1—Data obtained from prospective studies (Helmrich et al. (11), ◇; Hu et al. (13) Δ ○; Manson et al. (25) ▲; Manson et al. (26) ● ■; and Wannamethee et al. (40) □) examining the incidence of Type 2 DM as a function of varying levels of physical activity. The levels of physical activity are arbitrary and are derived from classification schemes developed by individual studies. With the exception of Manson et al. (26), all of the studies plotted observed a significant dose-response effect of increasing levels of physical activity on relative risk after adjusting for age and BMI.

in African-Americans (16). In this study, the risk of developing diabetes was reduced by 65% in blacks participating in moderate physical activity, after adjusting for age, sex, BMI, and waist/hip ratio. Physical activity was also inversely related to the incidence of diabetes in a group of Japanese-American men participating in the Honolulu Heart Program (3). Moreover, the age-adjusted 6-yr incidence in diabetes decreased with increasing quintiles of physical activity, lending further support for a dose-response effect of physical activity on diabetes prevention.

Perhaps the first large-scale diabetes prevention study to include physical activity as part of their intervention was a 6-yr feasibility study conducted in Malmö, Sweden (8). Men with impaired glucose tolerance (IGT) at baseline were nonrandomly assigned to either an intervention or control group. Exercise training consisted of two 60-min exercise sessions per week that included walking, jogging, and other recreational sporting activities. The intensity of exercise was not examined, and the intervention consisted of dietary manipulation combined with exercise, so that the separate effects of physical activity on the prevention of diabetes could not be directly ascertained. The conversion to diabetes in these IGT men was lower in the intervention group compared with the reference group (1.7% vs 4.6%, respectively). Glucose tolerance improved and 2-h insulin values decreased in the treatment group, whereas glucose tolerance worsened in the nontreated group. Moreover, the increase in cardiorespiratory fitness determined by an increase in maximal oxygen uptake was correlated with the improvement in glucose tolerance.

The Da Qing study conducted in China is considered to be the first randomized controlled trial to examine the effects of increased physical activity in the prevention of diabetes (29). Among 577 men with IGT, exercise and diet, either alone or in combination, decreased the rate of conversion from IGT to diabetes. Indeed, after adjusting for baseline BMI and fasting glucose, exercise decreased the risk for developing diabetes by 46%. Unfortunately, no attempt was made in this study to assess the possible dose-response effects of increased physical activity on the prevention of diabetes. However, this important study provides the first direct evidence that an increase in physical exercise decreases the risk for the development of diabetes.

To summarize the effects of physical activity on diabetes prevention, the evidence from the prospective studies clearly suggests that an increase in physical activity prevents or at least delays the development of Type 2 DM in adults. These prospective studies also provide some evidence that a dose-response effect of increasing physical activity on reducing the risk for Type 2 DM may indeed exist, although these data are not entirely overwhelming. To date, only one randomized controlled trial has been conducted to examine the effects of an increased physical activity on the prevention of Type 2 DM (29), but a dose-response analysis was not performed. Obviously, more of these powerful intervention studies are needed to further our understanding of the beneficial effects of physical activity in preventing this prevalent and serious disease. Fortunately, a large-scale randomized controlled trial is now underway in the United States. The Diabetes Prevention Program, a multicenter study that was begun in 1996, is designed to assess the effects of lifestyle intervention, including physical activity, on the prevention of Type 2 DM. In addition, and importantly, this study should determine whether a program of increased physical activity will help prevent progression

TABLE 4. Physical activity and the prevention of Type 2 DM: evidence from prospective studies, nonrandomized trials, and randomized controlled trials.

Study, Country	Study Design	Subjects	Treatment or Assessment	Study Duration	Exercise Intensity/Duration	Result
Manson et al., 1991 (25), United States	Prospective	87,253 women	Physical activity	8 yr	Vigorous; ≥1×/wk	↓ incidence of DM with ↑ in physical activity
Manson et al., 1992 (26), United States	Prospective	21,271 men	Physical activity	5 yr	Vigorous; ≥1×/wk	↓ incidence of DM with ↑ in physical activity
Helmrich et al., 1991 (11), United States	Prospective	5,990 men	Physical activity	14 yr	Weekly physical activity	↓ incidence of DM with ↑ in physical activity
Lynch et al., 1996 (24), Sweden	Prospective	1,038 men and women	Physical activity	4 yr	≥5.5 MET; ≥40 min	↓ incidence of DM
James et al., 1998 (16), United States	Prospective	318 men and 598 women; African-American	Physical activity	5 yr	Strenuous Moderate Low	↓ incidence of DM
Hu et al., 1999 (13), United States	Prospective	70,102 women	Physical activity	12 yr	Vigorous Regular walking	↓ incidence of DM
Wannamethee et al., 2000 (40), United Kingdom	Prospective	5,159 men	Physical activity	16.8 yr	Regular walking or cycling Recreational Sporting (vigorous)	↓ incidence of DM; ↓ risk of hyperinsuliemia
Eriksson et al., 1991 (7), Sweden	Nonrandomized controlled trial	Treated—181 IGT men Control—79 IGT men	Exercise + diet	6 yr	2 60-min sessions per wk	↓ incidence of DM; ↑ glucose tolerance
Pan et al., 1997 (29), China	Randomized, controlled trial	Exercise—141 IGT men Exercise + diet—126 IGT men Control—133 IGT men	Exercise only Exercise + diet	6 yr	↑ in units of exercise	↓ incidence of DM; No change in fasting glucose

DM, Type 2 diabetes mellitus; MET, metabolic equivalent (1 MET = resting metabolic rate); IGT, impaired glucose tolerance.

to diabetes in high-risk persons, such as those with obesity or a family history of diabetes.

It is clear from the available evidence that physical activity reduces the risk for development of Type 2 DM. Although the effects of exercise alone to improve glucose control in diabetes are not dramatic, the effects of physical activity on reducing cardiovascular risk factors in these patients are more obvious. Given the apparent association between these intermediate risk factors and mortality, the question that therefore arises is whether or not physical activity predicts mortality for patients with Type 2 DM. This question was recently addressed in a large prospective study by Wei et al.(41), who found that low cardiovascular fitness and physical inactivity independently predicted all-cause mortality in men with Type 2 DM. Moreover, this study demonstrated that the protective effect of cardiovascular fitness was the same in normal weight and overweight diabetic men. These data are the first to suggest the benefits of physical activity in diabetes extend beyond the effects on intermediate risk factors.

SUMMARY

An evidence-based review of the literature indicates that in patients with Type 2 DM, aerobic exercise or resistance training has a modest positive impact on glycemic control. Physiological studies indicate a somewhat more robust effect on insulin resistance of peripheral tissues, but given the complex pathophysiology of Type 2 DM, this impact may not be sufficient to translate into improved glucose control in many individuals with Type 2 DM. At the present time, there are not sufficient data to effectively address the issue of whether a dose-response relationship exists between exercise and improved metabolic control of Type 2 DM. Similarly, the impact of exercise training on blood sugar and lipids is relatively small, though generally positive.

In individuals at increased risk for the development of Type 2 DM, the research findings indicate a more robust impact of exercise in helping to prevent the onset of Type 2 DM. These data do indicate a dose-response effect of exercise to lower the risk for development of Type 2 DM. On the basis of recent data that increased fitness can reduce mortality in Type 2 DM, future research on the effectiveness of exercise in Type 2 DM should attempt to include assessment of additional cardiovascular risk factors beyond measures of glucose control and traditional lipoprotein levels.

RESEARCH QUESTIONS FOR FUTURE STUDIES

During the past decade, several additional classes of pharmacological agents have been approved (in the United States and elsewhere) for the treatment of Type 2 DM. However, there are very few, if any, data in the literature concerning the interaction, acute and chronic, between exercise and the insulin sensitization medications. Whether these medications enhance the effectiveness of exercise, or pose additional safety concerns, has not been adequately addressed.

Many studies of therapeutic effectiveness (pharmacological or otherwise) in Type 2 DM have moved from a position of measuring any amount of change from baseline to an attempt to evaluate whether a treatment, used singly or in combination with other modalities (e.g., other drugs), can prove effective in achieving recommended target goals of therapy (e.g., percentage of patients achieving HbA1c $< 7\%$). There are no studies of this nature using exercise in Type 2 DM.

In view of the data cited on positive effects of physical activity to decrease mortality and yet relatively modest effects on traditional cardiovascular risk factors, the most pressing research question is the mechanism that accounts for reduced mortality. The current literature contains very few data on the effects of exercise interventions on vascular health and disease in Type 2 DM.

Similarly, the medical literature in recent years has added substantially to our understanding of the association between adipose tissue distribution, insulin resistance, and cardiovascular risk, but there are relatively few data on the effects of exercise interventions, alone or in combination with diet interventions, to modulate cardiovascular risk through effects on adipose tissue distribution and components of the insulin resistance syndrome.

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Response of blood lipids to exercise training alone or combined with dietary intervention

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ABSTRACT

LEON, A. S., and O. A. SANCHEZ. Response of blood lipids and lipoproteins to exercise training alone or combined with dietary intervention. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., pp. S502–S515, 2001. **Purpose:** The purpose of this study is to review the effects of aerobic exercise training (AET) on blood lipids and assess dose-response relationships and diet interactions. **Methods:** We reviewed papers published over the past three decades pertaining to intervention trials on the effects of ≥ 12 wk of AET on blood lipids and lipoprotein outcomes in adult men and women. Included were studies with simultaneous dietary and AET interventions, if they had appropriate comparison groups. Studies were classified by the participants' relative weights expressed as mean BMIs. Information was extracted on baseline characteristics of study subjects, including age, sex, and relative baseline cholesterol levels; details on the training programs; and the responses to training of body weight, $\dot{V}O_{2max}$, and blood total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglyceride (TG). **Results:** We identified 51 studies, 28 of which were randomized controlled trials. AET was generally performed at a moderate to hard intensity, with weekly energy expenditures ranging from 2,090 to >20,000 kJ. A marked inconsistency was observed in responsiveness of blood lipids. The most commonly observed change was an increase in HDL-C (with reductions in TC, LDL-C, and TG less frequently observed). Insufficient data are available to establish dose-response relationships between exercise intensity and volume with lipid changes. The increase in HDL-C with AET was inversely associated with its baseline level ($r = -0.462$), but no significant associations were found with age, sex, weekly volume of exercise, or with exercise-induced changes in body weight or $\dot{V}O_{2max}$. **Conclusion:** Moderate- to hard-intensity AET inconsistently results in an improvement in the blood lipid profile, with the data insufficient to establish dose-response relationships. **Key Words:** EXERCISE, BLOOD LIPIDS, CHOLESTEROL, HDL, TRIGLYCERIDE

During the past three decades, there have been tremendous advances in the understanding of the role of blood lipids in the pathogenesis of atherosclerosis, the underlying cause of coronary heart disease (CHD), and related cardiovascular diseases (15). The 27th Bethesda Conference of the American College of Cardiology categorized LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), and triglycerides (TG) in risk factor categories I, II, and III, respectively (i.e., as risk factors for which interventions have been "proven to" (Category I), "are likely to" (Category II), or "might" (Category III) reduce incidence of CHD events (52). LDL, the principal carrier of cholesterol in the blood, plays a pivotal role in atherogenesis (62), with CHD risk progressively increasing with levels > 2.6 mmol·L^{-1} (>180 mg·dL^{-1}). The National Cholesterol Education Program (NCEP) (47) classifies a total cholesterol (TC) level of ≥ 6.2 mmol·L^{-1} (>240 mg·dL^{-1}) and an LDL-C level of ≥ 4.1 mmol·L^{-1} (>160 mg·dL^{-1}) as elevated, and TC levels of 5.2 mmol·L^{-1} to 4.0 mmol·L^{-1} (200–239 mg·dL^{-1}) and LDL-C levels of ≥ 34 mmol·L^{-1} (130 mg·dL^{-1}) as borderline high. In the presence of CVD or two or more other risk factors, borderline levels of TC and LDL-C are considered elevated. HDL-C appears to be independently and inversely related to severity of atherosclerosis and risk of CHD with levels ≤ 0.9 mmol·L^{-1} (≤35 mg·dL^{-1}) classified as "low" and levels ≥ 1.6 mmol·L^{-1} (≥60 mg·dL) as a "negative risk factor" or a protective factor against CHD (15,47,50). The possible independent relationship of plasma TG (and its principal carrier in the fasting state, very low density lipoprotein (VLDL)) to CHD is more complex and controversial (15,18,22,50). This is because elevated or borderline high levels of TG (>4.5 mmol·L^{-1} or >400 mg·dL^{-1} and 2.26–4.52 mmol·L^{-1} or 200–400 mg·dL^{-1}, respectively) generally do not occur as isolated entities. More commonly, they are associated with other metabolic disturbances and risk factors, including reduced HDL-C (15,23,50). TG-rich lipoprotein remnants also appear to be atherogenic, but less so than LDL (29,50).

A consensus also exists that physical inactivity and reduced cardiorespiratory endurance contribute to risk of CHD (49,53,79), with a sedentary lifestyle rated in Category II by the 27th Bethesda Conference (52). Among the multiple proposed mechanisms for the postulated protective effect of regular physical activity against CHD is a favorable effect on blood lipids, particularly an increase in HDL-C and a reduction in TG levels (50,54,79). Evidence support-

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ing this relationship has come from cross-sectional and longitudinal epidemiologic observational studies, as well as a growing number of experimental exercise training studies, and is further supported by small-scale metabolic studies demonstrating mechanisms for observed lipid changes. Such studies, which involved healthy, normal-weight, and obese men and women of all ages, as well as patients with diabetes, hypertension, and CHD, have previously been reviewed during the past two decades (5,8,13,17,38,39,45,54,67,69,76–78).

Cross-sectional observational studies, involving men and women of all ages performing a variety of aerobic activities, have consistently demonstrated what appears to be a positive dose-response association between volume and intensity of aerobic activities and plasma HDL-C levels and inverse associations with TG levels; however, causative relationships cannot be proven by such studies because of numerous potential confounding variables. These include possible genetic factors contributing to both a favorable lipid profile and self-selection of active lifestyles, and especially the contribution of a lower total body and abdominal fat mass in the more active individuals to increased HDL-C and reduced TG levels (13,38,66,81).

The focus of this review is on the results of published studies, which evaluated the effects of supervised endurance exercise conditioning programs on blood lipid and lipoprotein concentrations with identification of those that are randomized controlled trials (RCT). Specific questions that are addressed in this report include the following: 1) Does the available evidence support the hypothesis that endurance exercise training has a favorable influence on the blood lipid profile relative to future risk of CHD? 2) Does the blood lipid responses to training differ by the study subjects' sex, age, or race/ethnicity, and baseline lipid levels, and baseline relative body weight and its change with training? 3) Are the lipid responses to exercise related to the intensity, duration, the weekly volume of energy expenditure, the length of the endurance exercise program, and the associated changes with training in maximal oxygen uptake ($\dot{V}O_{2max}$)?

METHODS

For this review, an English language literature search from 1987 to the present was conducted via MEDLINE (National Library of Medicine, Bethesda, MD) and the Index Medicus, using as key words physical activity, exercise, blood lipids, and lipoproteins alone or in combination. Additional studies, particularly those published before 1987, were identified from references by previous reviewers. Since a consensus already exists that at least 12 wk of endurance exercise is required to have a training effect on blood lipids (49,66), this review was limited to studies of at least this length. Unless otherwise indicated, in the studies summarized in Tables 1–3, interventions consisted of supervised structured group aerobic exercise programs in sedentary, apparently healthy, white individuals. Included in these tables are a few studies in which monitored "lifestyle activities" and/or home exercises were also prescribed. A few studies also included resistance training.

A total of 51 studies were identified that met the above inclusion criteria. Of these, 28 were RCT. The studies are classified in Tables 1–3 by the participants' pretraining mean body mass index (BMI) levels, a format previously used by Stefanick (67). The BMI cutoff points of <25.0 $kg \cdot m^{-2}$ in Table 1, 25.0–29.9 $kg \cdot m^{-2}$ in Table 2, and ≥ 30 $kg \cdot m^{-2}$ in Table 3 are consistent with recent NHLBI Expert Panel recommendations for classifying people as normal weight, overweight, or obese, respectively (49). Studies cited are listed in chronological order and include the following information: number of subjects completing the studies, and their sex, age, and race/ethnicity if other than white; classification of baseline blood cholesterol and LDL-C levels on the basis of on NCEP guidelines (47); and any special health-related characteristics such as whether there was a nonexercise control group; details on the exercise training program, i.e., type(s) of exercise, length of the program, the peak intensity, frequency, and duration of exercise sessions, length of training, and an estimate of the weekly volume of energy expenditure, obtained either directly from published information, or more frequently calculated from the type of activity and the exercise prescription using the Ainsworth et al. (1) compendium of energy cost of specific activities and other interventions. Posttraining outcomes, in addition to whether there were any significant changes in TC, LDL-C, HDL-C, and TG, included changes in body weight and relative improvement in $\dot{V}O_{2max}$. Improvement in $\dot{V}O_{2max}$ ($mL \cdot min^{-1}$) was classified as low ($<10\%$), moderate (11–19%), or high ($\geq 20\%$). Exercise-induced change in body weight and blood lipids were compared by two-tailed t-tests for statistical significance with either the changes with training in the control group in the RCT or with baseline levels in uncontrolled studies.

We also attempted to identify from the study reports factors related to the study design, which may have affected blood lipid findings. These potential confounding variables included stability of diet and physical activity outside the study; hormonal status of women participants; the timing of the posttraining blood specimens for lipid assays relative to the last training session; and whether adjustments were made for possible plasma volume changes with training. The timing of blood samples relative to the last exercise session is relevant, since research has shown that a single prolonged exercise session may result in plasma volume alterations and acute metabolic responses, which can persist for up to 48 h after exercise (8,13,43,54,69). Reported lipid responses to acute endurance exercise include an increase in plasma HDL-C and a reduction in TG levels.

The strength of linear associations between percent change in the blood lipid/lipoprotein parameters and baseline and posttraining variables was made by Pearson product-moment correlation coefficients with statistical significance established at $P < 0.05$. Stepwise, multiple linear regression analyses also were performed to determine the percentage of the variability in blood lipid response to

training that could be explained by baseline and posttraining variables.

RESULTS

The 51 studies uncovered in this literature search, of which 28 were randomized RCT, are summarized in Tables 1–3 on the basis of the participants' baseline mean BMI categories. There were approximately 4700 participants (about 60% men), ranging in age from 18 to 80 yr (mean, 46.6 ± 0.35 yr), who successfully completed these studies. Study participants were predominately white, with only two studies including a sizable number of black subjects (35,44) and only two Asian subjects (46,72). On the basis of NCEP criteria (47), pretraining TC levels were classified as "elevated" in only nine of these studies (8,21,25,37,44,55,60,72,85), and in the remainder they were classified as either "normal" or "borderline high." Overall mean baseline lipid levels across studies were as follows: TC, 5.29 ± 0.85 mmol·L^{-1} (204.5 ± 33.9 mg·dL^{-1}); LDL-C, 3.53 ± 0.58 mmol·L^{-1} (136.5 ± 22.5 mg·dL^{-1}); HDL-C, 1.18 ± 0.24 mmol·L^{-1} (45.6 ± 9.3 mg·dL^{-1}); and TG, 1.41 ± 0.31 mmol·L^{-1} (125.0 ± 27.8 mg·dL^{-1}).

In almost all studies, exercise training was performed at a moderate to hard intensity, three to five times per week for 30 min or more per session, consistent with current ACSM guidelines for improving cardiorespiratory endurance in healthy adults (2). Only a limited number of studies directly compared the effects of more than one intensity of exercise on the blood lipid profile (8,11,31,49,70,74,85). The estimated weekly energy expenditure during structured exercise programs ranged from 2,090 kJ·wk^{-1} to >20,000 kJ·wk^{-1} (500 to >5,000 kcal·wk^{-1}), with a mean of 5,894.4 ± 3,450.5 kJ·wk^{-1} (1,408.8 ± 8,24.7 kcal·wk^{-1}) per study. None of the reported studies compared the effects of different volumes of exercise on blood lipids. The duration of exercise training ranged from 12 wk to 2 yr. Training generally resulted in significant improvements in $\dot{V}O_{2max}$ ranging from <3% to over 50%, with the mean increase across studies of 15.7%.

There was a considerable variability in body weight changes during training depending on whether there were concomitant dietary interventions. In a total of about 2200 subjects from 61 study groups in which there were no concomitant dietary changes, the change in body mass ranged from none to 7.2 kg, with a mean (± SD) change of −0.82 ± 1.38 kg. In contrast, in 15 studies involving overweight or obese subjects in which there were concomitant dietary interventions, the observed weight loss ranged from 7.2 to 17.9 kg.

A marked inconsistency in the response of blood lipids and lipoproteins to endurance exercise training was observed in all three weight categories. The most commonly observed lipid change was a significant ($P < 0.05$) increase in HDL-C. This was observed in men and women of all ages in 24 of the 51 studies (47%), including 20 studies without simultaneous dietary manipulations. In training groups (N = 61 involving about 2200 subjects) in which diet was held constant, the exercise-induced change in HDL-C ranged from a decrease of 5.8% to an increase of about 25%, with a mean increase of 4.6% across these studies ($P < 0.05$). Increases in HDL-C with training is reported to primarily involve the HDL_2 fraction and to be generally associated with an increase in lipoprotein lipase activity (13,43). Significant reductions in HDL-C levels were observed in two of the training studies reviewed involving overweight or obese participants in which there was a concomitant reduction in fat intake via a NCEP diet (21,37). It has been well documented by feeding experiments that a reduced saturated fat intake in addition to reducing targeted LDL-C also is likely to reduce HDL-C (and raise TG) levels in both black and white subjects (16,24). Observational studies also have shown that populations consuming low-fat diets have both low HDL-C and LDL-C; however, they also invariably have low CHD rates (35). Furthermore, it appears from this review that aerobic exercise training negates or attenuates this dietary-induced reduction in HDL-C, particularly if there is an associated substantial weight loss, i.e., ≥ 4 kg (25,68,85).

Significant reductions in LDL-C, TG, and TC with exercise training were observed less frequently than an increase in HDL-C. Exercise training in the absence of simultaneous dietary interventions resulted in mean reductions in TG, LDL-C, and TC of about 3.7% ($P < 0.05$), 5.0% ($P < 0.05$), and 1.0% (P = NS), respectively, across studies. Men generally had a greater reduction in TG levels than the women participants. Concurrent reductions in dietary fat intake and/or a hypocaloric diet potentiated the reduction in these three lipid parameters; however, as previously mentioned, a concomitant reduction in fat intake also reduced HDL-C levels, with the reduction being partially attenuated by simultaneous exercise training and/or weight reduction. Thus, this review confirms the observations of previous reviewers of a marked inconsistency in blood lipid changes with endurance exercise training with an increase in HDL-C noted in only about half of the reported studies. A great deal of heterogeneity in the response to the same training stimulus also has been observed within studies. For example, in the HERITAGE Family Study (43) summarized in Table 2, 20 wk of a standardized and supervised exercise program in a large heterogeneous population resulted in a mean increase is HDL-C of 3.6%; however, further analyses showed that the change ranged from a reduction in HDL-C from baseline levels of 0.11 mmol·L^{-1} (4.2 mg·dL^{-1}) or 9.3% in Quartile 1 to an increase of 0.18 mmol·L^{-1} (6.9 mg·dL^{-1}) or 18% in Quartile 4 (Leon et al., unpublished data). This heterogeneity in response was similar for both sexes, blacks and whites, and offspring and parents.

A myriad of potential confounding variables, undoubtedly contributing to this variability in responsiveness of blood lipids to exercise training, are summarized in Table 4. Space limitations prohibit a detailed discussion of how these potential confounding variables may have influenced the outcomes of the studies summarized in this report. However, it should be pointed out that genetic variations are most likely important contributors to this variability. For example, in the HERITAGE Family Study, heritability was

TABLE 1. Blood lipid responses to aerobic exercise training in studies involving sedentary normal weight participants (BMI < 25 kg · m^{-2})

Literature Citation	Subjects/Groups	Exercise Training Program: Mode	Length	Intensity/Frequency Duration/Volume(kJ · wk^{-1})	Δ Body Weight/Δ $\dot{V}O_{2max}$*	ΔBlood Lipids
Huttunen et al., 1979 (25)	*N* = 90 men, 40–45 yr with elevated TC; exercise vs. control (RCT)	Walking, jogging, swimming	16 wk	40–60% HRR; 3×/wk; 30 min; 3570	NSΔ; Small inc. $\dot{V}O_{2max}$	Inc. HDL-C ($P < 0.01$) Dec. TG ($P < 0.05$) NSΔ TC, LDL-C
Wood et al., 1983 (83)	*N* = 79 men, 18–24 yr with BL high TC; Exercise vs. control (RCT)	Walking or jogging	1 yr	70–85% $\dot{V}O_{2max}$; 3–5×/wk; 25 min; 4789	1.9 kg ($P < 0.01$); Large inc. $\dot{V}O_{2max}$	NSΔ
Thomas et al., 1985 (75)	*N* = 36 men, 18–25 yr with normal TC; 1. Exercise: continuous 2. Exercise: intervals (4 min exer/4 min rest) 3. Exercise: intervals (2 min exer/3 min rest) 4. Control (RCT)	Jogging/running (8 km per session)	11 wk	75–85% HR max— Continuous: 90–100% HR max— Interval: 3×/wk; 60 min; 6276–6904	NSΔ; 1. Small inc. $\dot{V}O_{2max}$ 2. Moderate inc. $\dot{V}O_{2max}$ 3. NSΔ $\dot{V}O_{2max}$	NSΔ;
Santiago et al., 1987 (58)	*N* = 25 women, 22–40 yr with normal TC; 1. Exercise (walkers) 2. Exercise (runners) 3. Control (RCT)	Treadmill walking or running	20 wk	84% HR max; 4×/wk; 51–55 min (walkers), 32–36 min, (runners); 5778	NSΔ; Large inc. $\dot{V}O_{2max}$	NSΔ
Stein et al., 1990 (70)	*N* = 49 men, 44 yr with BL high TC; 1. Moderate intensity 2. Intermediate intensity 3. High intensity 4. Control (RCT)	Cycle ergometer	12 wk	1. 65% HR max 2. 75% HR max 3. 85% HR max; 3×/wk; 30 min; 2071–3766	NSΔ; Moderate inc. $\dot{V}O_{2max}$ in groups 1, 2 and high inc. group 3	Inc HDLC-C in Groups 2, 3 but not 1 ($P < 0.01$) Dec. LDL-C group 2 only ($P < 0.05$) NSΔ*TC, TG*
Duncan et al., 1991 (11)	*N* = 53 women, 29–40 yr (17% Black, 2% Hispanic) with normal TC; 1. 'Aerobic walking,' 8 km. hr^{-1}. 2. 'Fast walking', 6.4 kg · hr^{-1} 3. Strolling (4.8 km · hr^{-1}) 4. Control (RCT)	Walking (4.8 km per session)	24 wk	Intensity, NR; 5×/wk; 30–60 min; 6326	NSΔ; Small inc $\dot{V}O_{2max}$ groups 1, 2 and moderate inc. group 3 ($P < 0.05$)	Inc. HDL-C in groups 1 and 3 ($P < 0.05$) Dec. LDL-C in group 2 NSΔ TC, TG
Motoyama et al., 1995 (46)	*N* = 15 men + 15 women (Japanese), 65–83 yr with hypertension, diabetes, and BL high TC; exercise vs. control (RCT)	Treadmill walking	36 wk	At lactate threshold; 3–6×/wk (mean, 5.2); 30 min; 3226	NSΔ;Δ$\dot{V}O_{2max}$ NR	Inc. HDL-C ($P < 0.001$) NSΔ TC, LDL-C, TG
Santiago et al., 1995 (59)	27 women, 22–40 yr with normal TC and high HDL-C; exercise vs. control (RCT)	Treadmill walking (5.8 km · hr^{-1} 7% grade)	40 wk	Mean 72% HR max; 4×/wk; 53–56 min; 5778	NSΔ; Large inc. $\dot{V}O_{2max}$	NSΔ
Leaf et al., 1997 (36)	76 men, 23–68 yr with BL high TC; BL high TC; exercise (no control)	Worksite fitness program: treadmill program: treadmill running, cycle ergometer, stair-climber, rowing machine + ↑ LTPA encouraged	1 yr 1 yr	60–80% HRR; Frequency/duration NR; 8309	NSΔ; Small inc. $\dot{V}O_{2max}$ Small inc. $\dot{V}O_{2max}$	Inc. HDL-C ($P < 0.05$) NSΔ TC, LDL-C, TG NSΔ TC, LDL-C, TG
Sunami et al., 1999 (71)	20 men + 20 women (Japanese), 60–70 yr, with BL high cholesterol; 1. Exercise 2. Control (RCT)	Cycle ergometer	20 wk	50% $\dot{V}O_{2max}$; 2–4 wk 60 min; 4460	NSΔ; Small inc. $\dot{V}O_{2max}$	Inc. HDL-C ($P < 0.05$) NSΔ TC, LDL-C, TG

RCT, randomized control trial; NSΔ, no significant difference between the changes with training in the treatment and control group or from baseline if there is no control group; HRR, heart rate reserve; LTPA, leisure time physical activity; BL, borderline; inc, increase; Dec, decrease.

* Δ$\dot{V}O_{2max}$ = relative percent change in $\dot{V}O_{2max}$ (L · min^{-1}): 'small' (≤ 10%), medium (10–19%), or large (≥ 20%).

TABLE 2. Plasma lipid changes in studies involving exercise training in sedentary, overweight participants (BMI 25–29.9 kg · m^{-2})

Literature Citation	Subjects/Groups	Exercise Training Program: Mode	Length	Intensity/Frequency Duration/ Volume(kJ · wk^{-1})	Δ Body Weight/Δ $\dot{V}O_{2max}$*	ΔBlood Lipids
Leon et al., 1984 (41)	N = 48 men with Type 2 DM, 33–69 yr with BL high cholesterol and TG; 5 exercise groups (no control)	Treadmill walking	12 wk	50–70% HRR; 2–4×/wk; 30–60 min; 1004–5021	NSΔ; Small inc. $\dot{V}O_{2max}$ all groups	NSΔ
Sopko et al., 1985 (64)	N = 21 men, 19–44 yr with normal TC;	Treadmill walking; or jogging (44–60 km · wk^{-1})	15 wk (last 3 wk with weight stable in groups 2 and 3)	6 METs with HR 145–155 bpm; 5×/wk; duration, NR; 14,644	−6 kg, groups 2 and 3 (P < 0.001); small inc. $\dot{V}O_{2max}$ groups 2 and 3	1. Inc. HDL-C > group 2 than group 1 and group 3 (P < 0.01)
	1. Exercise-weight constant					2. Dec. TC, LDL-C group 2 (P < 0.01)
	2. Exercise-weight loss					3. Dec. TG group 2 (P < 0.01)
	3. Hypocaloric diet-weight loss					
	4. Control (RCT)					
Cauley et al., 1987 (7)	N = 203 postmenopausal women; 57.7 yr with BL high TC;	Unsupervised walking groups (4.8 km per session recommended or 11.3 km · wk^{-1} minimum)	24 mo	Intensity, NR; 3×/wk; duration, NR; 6397 (from PA logs)	NSΔ; NR Δ$\dot{V}O_{2max}$	NSΔ
	1. Exercise, community-based (PA logs monitored)					
	2. Control (RCT)					
King et al., 1991 (30)	N = 168 men + 132 women, 50–65 yr with normal TC men, and BL high TC women;	Walking and/or jogging	12 mo	Moderate-intensity: 60–70% HR max; 5×/wk; 30 min	NSΔ; Small inc. $\dot{V}O_{2max}$ groups 1–3 (both sexes)	NSΔ
	1. Hard-intensity, supervised			Hard-intensity: 73–88% HR max; 3×/wk; 40 min; 5448 for men. 4602 for women		
	2. Hard-intensity home-based					
	3. Moderate-intensity, home-based					
	4. Control (RCT)					
Wood et al., 1991 (85)	N = 119 men; 112 women), 25–49 yr with elevated TC;	Brisk walking or jogging	12 mo	60–80% HR max; 3×/wk; 45 min; 4607 men, 4439 women	1. −5.1 kg	Inc. HDL-C group 1 (P < 0.01).
	1. Exercise + hypocaloric step 1 NCEP diet			2. −4.1 kg	Dec. TC, LDL-C groups 1 and 2 (P < 0.01)	
	2. Hypocaloric Step 1 NCEP diet				3. −1.3 kg (P < 0.01); medium inc. $\dot{V}O_{2max}$ group only	Dec. TG group 1 (P < 0.05)
	4. Control (RCT)					
Hellenius et al., 1993 (21)	N = 157 men, 30–60 yr with elevated TC;	Walking and or jogging	24 wk	75–85% HRR: 4×/wk; 30–50 min; 3013–5021	NSΔ; NR (Dec. HR 4% at 150 W)	Inc. LDL-C groups 2 and 3 (P < 0.05)
	1. Exercise					NRΔ HDL-C, TG
	2. Reduced-fat diet					
	3. Exercise + same diet					
	4. Control (RCT)					
Seip et al., 1993 (61)	N = 28 men + 29 women, 60–72 yr with normal to BL high TC; exercise vs. control (RCT)	Walking, jogging, and/or cycle ergometer	9–12 mo	80–89% HR max: 3–5×/wk; 45–60 min; 7590 men, 5004 women	−2.6 kg men (P < 0.002).	Inc. HDL-C (p = 0.003)
					−2.4 kg women (P < 0.003); medium inc. $\dot{V}O_{2max}$	Dec. TC, LDL-C (P < 0.05)
						Dec. TG (P < 0.0001)

TABLE 2. *Continued*

Literature Citation	Subjects/Groups	Exercise Training Program: Mode	Length	Intensity/Frequency Duration/ Volume(kJ · wk^{-1})	Δ Body Weight/Δ $\dot{V}O_{2max}$*	ΔBlood Lipids
Lindheim et al., 1994 (44)	N = 95 women (postmenopausal), 42–59 yr with BL high TC and high HDL-C; 1. Exercise 2. Hormone therapy replacement (HRT) 3. Exercise + HRT 4. Control (RCT)	Treadmill walking and cycle ergometer	24 wk	70% HR max; 3×/wk; 30 min; 2322	NSΔ; Small inc. $\dot{V}O_{2\ max}$ groups 1 and 3	Inc. HDL-C groups 2 and 3 ($P <$ 0.01) Dec. TG group 1 ($P < 0.05$) Inc. TG group 3 ($P < 0.05$)
Williams et al., 1994 (82)	N = 130 men, 30–59 yr with TC NR: 1. Exercise 2. Hypocaloric diet 3. Control (RCT)	Brisk walking and/or running	12 mo	60–80% HR max; 4×/wk, 40–50 min; 5622	–1.3 kg group 1, –2.2 kg group 2 ($P < 0.005$); NRΔ $\dot{V}O_{2max}$	Inc. HDL group 2 > group 1 ($P < 0.05$) (Inc. HDL-C > in those with high baseline HDL-C) Other lipids NR
King et al., 1995 (31)	N = 114 men + 93 women, 50–65 yr with BL high LDL-C; 1. Hard-intensity supervised exercise 2. Hard-intensity home-based exercise† 3. Moderate-intensity home-based exercise† 4. Control (RCT), †PA logs monitored	Walking or jogging	24 mo	Hard-intensity: 60–73%, HR max; 3×/wk; 30 min; Moderate-intensity: 73–80%, 5×/wk; 40 min; 3013	NSΔ; small inc. $\dot{V}O_{2\ max}$ groups 1–3	NSΔ
Leon et al., 1996 (40)	N = 22 men, 22–4 yr with normal TC; exercise vs control (RCT)	Stair climbing and treadmill walking	12 wk	Intensity, NR; stairs: 10 floors self-paced + 45 min on treadmill at 5.15 km·hr^{-1} and 2% grade: 5×/wk; 8386	NSΔ; NSΔ $\dot{V}O_{2max}$	NSΔ
Ready et al., 1996 (56)	N = 56 women, >50 yr (mean, 61.3) with BL high TC; 1. Exercise 2. More exercise 3. Control (RCT)	Treadmill walking	24 wk	60% $\dot{V}O_{2max}$ peak; group 1: 3×/wk, group 2: 5×/wk. 60 min; 4,753 (group 1), 12,611 (group 2)	–0.6 kg group 1, ($P <$ 0.05); NSΔ group 2; small inc. $\dot{V}O_{2max}$ group 1: moderate inc. $\dot{V}O_{2max}$ group 2	NSΔ
Crouse et al., 1997 (8)	N = 26 men, 47 yr-with elevated TC; 1. Hard-intensity exercise 2. Moderate-intensity exercise (no control)	Cycle ergometer	24 wk	Hard-intensity: 80% $\dot{V}O_{2max}$ Moderate-intensity: 50% $\dot{V}O_{2max}$ 3×/wk;duration, NR; 4393	–1.2 to –1.5 kg ($P <$ 0.05); large inc. $\dot{V}O_{2\ max}$ groups 1 and 2	NSΔ
Katzel et al., 1997 (28)	N = 21 men, 46–80 yr (mean, 59) with normal TC, low HDL-C; 1. Exercise	Treadmill walking and cycle ergometer	36 wk	70–80% HRR; 3×/wk; 30–45 min; 4359	NDΔ group 1 36 wk; –8.1 kg group 2 ($P < 0.1$); Moderate inc. $\dot{V}O_{2\ max}$ groups 1 and 2	NSΔ HDL-C group 1, Inc. HDL group 2 ($P < 0.01$) Dec. TC, LDL-C group 2 ($P <$ 0.05) NSΔ TG

TABLE 2. *Continued*

Literature Citation	Subjects/Groups	Exercise Training Program: Mode	Length	Intensity/Frequency Duration/ VOVolume(kJ · wk^{-1})	Δ Body Weight/Δ $\dot{V}O_{2max}$*	ΔBlood Lipids
	2. Exercise + addition of hypocaloric phase 1 AHA diet (no control)					
Kraemer et al., 1997 (35)	*N* = 31 women, 35 yr with baseline TC NR;	Treadmill walking, jogging, cycle ergometer, rowing, and stair climber + strength training	12 wk	70–80% HR max; 3×/wk; 30–45 min; 4079; 10 resistance exercises, moderate to hard	–6.2, –6.8, –7.0 kg groups 1–3 respectively; Large inc. $\dot{V}O_{2max}$ groups 2 and 3	Dec. HDL-C groups 1 and 3 ($P < 0.05$)
	1. Hypocaloric low-fat diet					Dec. LDL-C, TC groups 2 and 3 ($P < 0.05$)
	2. Above diet + aerobic exercise					NSΔ TG
	3. Above diet +					
Thompson et al., 1997 (76)	*N* = 17 men, 40 yr with BL high TC; (no control)	Walking, jogging or cycle ergometer	12 mo	60–80% HR max; 4×/wk; 50 min; 8130	High inc. $\dot{V}O_{2max}$	Inc. HDL-C ($P < 0.05$).
						LDL-C ($P < 0.05$).
						NSΔ TC, TG
Grandjean et al., 1998 (19)	*N* = 21 women, 36.3 yr and 16 women, 67.6 yr with normal TC; exercise (no control)	Brisk walking or jogging	12 wk	79% $\dot{V}O_{2max}$; 4–/wk; 26–53 min and 33–73 min for young and older women, respectively; 5020	NSΔ; moderate inc. $\dot{V}O_{2max}$	Dec HDL-C ($P < 0.05$)
						NSΔ TC, LDL-C, TG
Klenbanoff et al., 1998 (32)	*N* = 18 postmenopausal women (10 on HRT), 45–61 yr (mean, 52.7) with normal TC; exercise (no control)	Walking, stair-stepping, rowing, cycle ergometer, and/or aerobic dance	12 wk	70–75% $\dot{V}O_{2max}$; 3–4–/wk; 30–50 min; 4184–5439	NSΔ; small inc. $\dot{V}O_{2max}$	NSΔ
Schuit et al., 1998 (60)	*N* = 113 men + 116 women, 60–80 yr with elevated TC;	Cycle ergometer (home-based); ball games, aerobic dance, (supervised)	24 wk	Supervised: 70% $\dot{V}O_{2max}$; 4×/wk; 45 min;	NSΔ; Inc. peak power output groups 1 and 2	NSΔ
	1. Home-based exercise			Home-based: intensity NR; 3×/wk; 30 min; 4151 (supervised) and 3770 (home-based)		
	2. Supervised exercise					
	3. Control (RCT)					
Stefanick et al., 1998 (68)	*N* = 177 women, 45–64 yr + 90 men, 30–64 yr with BL high TC and low HDL-C (men);	Brisk walking or jogging (supervised + additional home-based exercise for minimum of 16 km · wk^{-1}	12 mo	Intensity, NR; 3×/wk; duration, NR; 4184	Women: –2.7 kg group 2, –3.1 kg group 3	Dec. TC ($P < 0.003$), and Dec.
	1. Exercise				Men: –2.8 kg group 2, –3.1 kg group 3 ($P < 0.001$); small inc. $\dot{V}O_{2max}$ groups 1 and 3	LDL-C ($P = 0.0004$) group 3 only
	2. NCEP step 2 diet					NSΔ HDL-C, TG
	3. Same diet + exercise					–3.1 kg group 3
	4. Control (RCT)					
Vasankari et al., 1998 (80)	*N* = 34 men, 34–52 yr + *N* = 70 women, 31–58 yr, with BL high TC; exercise (no control)	Walking (70% of exercise time), plus ski machine, cycle ergometer, dancing, circuit training (supervised 3×/mo + home-based with PA log)	40 wk	HR 110–145 bpm; frequency, NR; 209 min · wk^{-1} (women) and 257 min · wk^{-1} (men); 4184	–2.9 kg (men) –1.8 kg (women) ($P < 0.0001$); Moderate, inc. $\dot{V}O_{2\ max}$	Inc. HDL-C in both men ($P > 0.001$) and women ($P < 0.001$)
						Dec. LDL-C in both men ($P < 0.01$) and women ($P < 0.001$), NSΔ TC, TG

TABLE 2. *Continued*

Literature Citation	Subjects/Groups	Exercise Training Program			Δ Body Weight/Δ $\dot{V}O_{2max}$*	ΔBlood Lipids
		Mode	Length	Intensity/Frequency Duration/ Volume(kJ · wk^{-1})		
Zmuda et al., 1998 (86)	*N* = 17 men, 26–49 yr (mean, 39) with normal to BL high TC and low to normal HDL-C;	Walking, jogging, cycle ergometer	12 mo	60–90% HR max; 4×/wk; 50 min; 8540	NSΔ (weight held constant); large inc. $\dot{V}O_{2max}$	Inc. HDL-C in men with normal HDL-C, but not in those with low HDL-C ($P < 0.0001$), NSΔ TC, LDL-C, TG
	1. Exercise below average HDL at baseline 2. Exercise normal HDL at baseline (no control)					
Spate-Douglas and Keyser 1999 (65)	*N* = 25, women, 40 yr with normal TC and low HDL-C;	Walking (home-based with PA logs)	12 wk	Group 1: 80% HRR	NSΔ Small inc. $\dot{V}O_{2max}$ groups 1 and 2	Inc. HDL-C in both groups ($P <$ 0.05) with NS difference between groups ΔTC, LDL, TG NR
	1. High-intensity exercise			Group 2: 60% HRs; 3×/wk; 3.2 km per session; 2669		
	2. Moderate-intensity exercise (no control)					
Dunn et al., 1999 (12)	*N* = 116 men + 119 women 46 yr with BL high TC;	Individual aerobic activities (type NR)	24 mo	Group 1: 50–85% $\dot{V}O_{2\ max}$; 3–5×/wk; 20–60 min; group 2: 'at least 30 min,' moderate-intensity PA 'on most, preferably all, days of the week'; 3473 (group 1)	NSΔ; small inc. $\dot{V}O_{2\ max}$ groups 1 and 2	Inc. HDL-C Group 1 ($P = 0.02$)
	1. 'Structured' exercise					Dec. TC, LDL-C Group 1 ($P <$ 0.05) NSΔ TG
	2. 'Lifestyle' exercise (no control)					
Leon et al., 2000 (43)	*N* = 299 men + 376 women, 17–65 yr (black and white) with normal TC and low HDL-C; exercise (no control)	Cycle ergometer	20 wk	75% $\dot{V}O_{2\ max}$ 3×/wk; 50 min, 4117	−0.42 kg (men), −0.18 kg (women) ($P < 0.05$); Moderate inc. $\dot{V}O_{2max}$	Inc. HDL-C both sexes and races NSΔ TC, LDL

Dec. TG men only ($P < 0.05$) RCT, randomized controlled trial; NSΔ, no significant difference between the changes with training in the treatment and control group or from baseline if there is no control group; HR max, highest heart rate attained during baseline exercise testing; NR, not reported in manuscript; HRR, heart rate reserve; HRT, hormone replacement therapy; Inc., increase; Dec., decrease.

* $\Delta\dot{V}O_{2max}$ = percent increase in $\dot{V}O_{2max}$ (L·min^{-1} with small (≤ 10%), moderate (11–19%), large (≤ 20%).

TABLE 3. Blood lipid responses to endurance exercise training in studies involving Sedentary, obese participants (BMI ≥30 kg · m^{-2})

Literature Citation	Subjects/Groups	Exercise Training Program: Mode	Length	Intensity/Frequency Duration/Volume(kJ · wk^{-1})	Δ Body Weight/Δ $\dot{V}O^{2max}$*	ΔBlood Lipids
Andersen et al., 1995 (3)	N = 66 women, 43.6 yr with BL high TC;	Aerobic: Step aerobics	48 wk	Aerobic: Borg Scale 11–15 (moderate- to heavy-exertion range); 3×/wk; 40 min; Strength: ≥ 10 repetitions 3×/wk; 40 min; 4895	Group 1:–3.1 kg	NS_2ΔHDL
	1. Hypocaloric 'balanced-deficit diet'	Resistance: large muscle groups strength training			Group 2: 13.4 kg	Dec. TC and LDL-C
	2. Same diet + aerobic and resistance exercise				Group 3: 17.9 kg	Groups 2–4 ($P < 0.005$)
	3. Same diet + resistance exercise				Group 4:–15.3 kg ($P < 0.005$) differences between groups); Δ$\dot{V}O_{2max}$ NR	Dec. TG group 2 only ($P < 0.05$)
	4. Same diet + aerobic exercise (no control)					
Katzel et al., 1995 (27), 1997 (28)	N = 111 men, 46–80 yr (mean, 61) with normal TC;	Treadmill walking/running and cycle eregometer	36 wk	70–80% HRR; 3×/wk; 30–40 min; 4389	Group 1–9.5 kg ($P < 0.01$)	Inc. HDL-C group 1 ($P < 0.05$)
	1. Hypocaloric AHA phase 1 diet (weight-loss group)				Group 2:–0.6 kg (NS)	Inc. TC, LDL-C and TG
	2. Exercise + isocaloric AHA phase 1 diet				Group 1 vs 2 ($P < 0.05$); Moderate inc. $\dot{V}O_{2max}$ group 2	Group 3 ($P < 0.05$)
	3. Control (RCT)					NSΔ TC, LDL-C, TG in groups 1 and 2
Ready et al., 1995 (55)	N = 25 women 62.5 yr with elevated TC;	Walking	24 wk	54% HRR; 5×/wk; 50–60 min; 6368	NSΔ; small inc. $\dot{V}O_{2max}$	Dec. TC and TG ($P < 0.05$)
	1. Exercise					NSΔ HDL-C, LDLC
	2. Control (RCT)					
Fox et al., 1996 (14)	N = 40 postmenopausal women, 65.6 yr with BL high TC;	Walking + strength training	24 wk	Aerobic training: 60–70% HRR; 3×/wk; 60 min	Group 1: –6.6 kg ($P < 0.05$)	NSΔ
	1. Hypocaloric diet (–2092 kJ · day^{-1})			Strength training: 12 muscle groups, 2×/wk; 80% 1 RM, one repetition; 8867	Group 2: –5.8 kg ($P < 0.05$)	
	2. Hypocaloric diet (–2929 kJ · day^{-1})				Group 3: –7.1 kg ($P < 0.05$)	
	3. Hypocaloric diet (–2092 kJ · day^{-1}) + exercise (aerobic and resistance) (no control)				Group 1 vs 2 vs 3 (NS); Δ$\dot{V}O_{2max}$ NR	
Nicklas et al., 1997 (51)	N = 46 men 46–72 yr (mean 57) with normal TC;	Treadmill walking/ergometer and/or ski machine (all groups)	36 wk	70–80% HRR; 3×/wk; 60 min; 3929–4707	NSΔ moderate inc. $\dot{V}O_{2max}$ groups 1 and 3	Inc. HDL-C groups 1 and 2 ($P < 0.05$) (Inc. HDL-C group 1
	1. Normal weight exercise group (BMI) 22–26)				High inc. $\dot{V}O_{2max}$ group 2	Dec. TG all groups ($P < 0.05$) with NS difference between groups
	2. Overweight exercise group (BMI 27–30)					Dec. TC, LDL-C group 3 only ($P < 0.05$)
	3. Obese exercise group (BMI 31–37) (no control)					
Snyder et al., 1997 (63)	N = 13 women, 43 yr with normal TC; exercise (no control)	Brisk walking	32 wk	50–60% HRR; 3×/d; 5 d · wk^{-1} (monitored by daily PA records); 5205	NSΔ; NSΔ $\dot{V}O_{2max}$	NSΔ
Kokkinos et al., 1998 (34)	N = 34, black men with hypertension (on antihypertensive medications), 35–76 yr (mean, 58), with BL high TC;	Cycle ergometer	16 wk	60–80% predicted HR max; 3×/wk; 20–50 min; 1255–3138	NSΔ; Δ$\dot{V}O_{2max}$ NR	NSΔ
	1. Exercise					
	2. Control (RCI)					

TABLE 3. *Continued*

Literature Citation	Subjects/Groups	Exercise Training Program: Mode	Length	Intensity/Frequency Duration/ Volume(kJ · wk^{-1})	Δ Body Weight/Δ $\dot{V}O_{2max}$*	ΔBlood Lipids
Anderson et al., 1999 (4)	N = 33 women, 21–60 yr (mean, 42.9) with BL high TC;	Structured: step aerobics	68 wk	Structured: 7–11 METs (1883–2092 kJ for session); 3×/wk; 45 min; 5649–6276	Group 1: −8. 7 kg ($P < 0.01$) Group 2: −7.9 kg ($P < 0.01$) (Group 1 vs 2 NS);	Dec. TC in groups 1 and 2 (group 1 vs 2 NS)
	1. Hypocaloric, low fat diet + 'structured exercise'	Lifestyle: ↑ PA by 30 min throughout the day/most days of the week (monitored by accelerometers)			$\Delta\dot{V}O_{2max}$ NR	NSΔ HDL-C, LDL-C, TG in either group
	2. Same diet + 'lifestyle-activity' (no control)			Lifestyle: Increase of 979 kJ · d^{-1} of PA		
Hagberg et al., 1999 (20)	N = 51 men, 45–80 yr (mean, with normal TC; exercise (no control)	Treadmill walking, jogging, cycle ergometer	16 wk	70–80% $\dot{V}O_{2max}$; 3×/wk; 45 min; 4293	NSΔ; moderate inc. $\dot{V}O_{2max}$	Inc. HDL-C only in subject APO E_2 phenotype (N = 33) ($P < 0.01$) Dec. TG only in subjects with APO E_2 ($P < 0.01$) NSΔ TC, LDL-C

RCT randomized controlled trial; NSΔ, no significant differences between the changes with training in the treatment and control group or from baseline if there is no control group; HRR, heart rate reserve; LTPA, leisure time physical activity; BL, borderline; NR, not reported in manuscript; HR max, highest heart rate attained during baseline exercise testing.
* $\Delta\dot{V}O_{2max}$ = percent increase in $\dot{V}O_{2max}$ (L · min^{-1}) with small (≤10%), moderate (11–19%), large (≥20%).

TABLE 4. Potential factors contributing to variability in the reported blood lipid responses to exercise training

Biological factors
Genetic differences
Race/ethnicity
Age
Sex
Hormonal status
Day-to-day and seasonal fluctuations in blood lipids
Behavioral and lifestyle characteristics (baseline and changes during exercise training)
Socioeconomic status
Dietary habits
Alcohol intake
Cigarette smoking
Medication use
Contraceptive or hormone replacement therapy
Physical activity aside from the training program
Physiologic characteristics (baseline and changes with training)
Blood lipid levels
Body weight, and fat mass and its distribution
$\dot{V}O_{2max}$ and submaximal exercise capacity
Study Design
Adequacy of sample size relative to the expected size and heterogeneity of the study effect
Control group and randomization
The exercise prescription, including intensity, duration, weekly volume of exercise, and length of training program
Extent of supervision and adherence to training, constancy in life habits, medication use, etc.

found to be a relatively strong contributor to both baseline blood lipids (9) and their responsiveness to exercise training (Rice et al., unpublished data). In addition, methodological flaws were noted in many of the studies surveyed in this report. These include absence of a control group to detect possible laboratory drift and seasonal fluctuations in blood lipid levels; only single blood specimens being obtained before and after training with the timing of the posttraining specimen often ≦ 24 h after the last exercise sessions (and therefore perhaps reflecting lipid changes caused by acute plasma volume or metabolic changes) and over half of the listed studies not even reporting the timing of the posttraining specimen(s); failure to consider the phase of the menstrual cycle in drawing blood before and after training in all but a limited number of the studies involving eumenorrheic women (43,55,59); failure to adjust for possible exercise-induced plasma volume changes in most studies; and possible inadequate control in dietary habits, alcohol intake, smoking, and levels of routine daily physical activity levels during the exercise training phase. The importance of monitoring physical activity aside from the exercise program is illustrated in a study in Table 2 by Leon et al. (40) designed to provide 2000 kcal·wk^{-1} (8370 kJ·wk^{-1}) of aerobic exercise. Repeated leisure-time physical activity (LTPA) questionnaires revealed that the participants had substantially reduced their usual LTPA during the exercise program, which probably contributed to the failure to achieve a lipid response.

Table 5 shows Pearson correlation values (r) between percent changes in blood lipid parameters and baseline and posttraining variables. This analysis is limited to groups from the studies listed in Tables 1–3, which performed exercise without concomitant dietary changes (N = 61 involving about 2200 subjects). A significant (two-tailed) inverse association was

TABLE 5. Correlations of baseline and posttraining variables with changes in blood lipids (N = 61 study groups involving about 2200 participants)

Variable	Percent Changes with Training			
	TC	LDC-C	HDL-C	TG
Pretraining				
Age (yr)	−0.219	−0.183	−0.038	−0.154
Weight (kg)	−0.110	−0.124	0.182	−0.439**
BMI ($kg \cdot m^{-2}$)	−0.006	−0.013	0.130	−0.313*
$\dot{V}O_{2max}$ ($L \cdot min^{-1}$)	−0.216	−0.249	0.103	−0.439**
TC	−0.269	−0.094	0.024	−0.077
LDL-C	−0.420**	−0.232	−0.067	−0.065
HDL-C	−0.148	0.027	−0.462**	0.348*
TG	−0.297	−0.139	0.164	0.−290*
Wks of training	−0.137	−0.330*	−0.073	0.081
Exercise volume ($kJ \cdot wk^{-1}$)	0.205	−0.045	0.078	−0.097
Posttraining				
Weight loss (kg)	0.415**	0.381**	−0.227	0.443**
$\Delta\dot{V}O_{2max}$ (%)	0.027	0.196	0.222	−0.084
ΔTC	1.00	0.800**	−0.154	0.550**
ΔLDL-C	0.800**	1.00	−0.402**	0.128
ΔHDL-C	−0.154	−0.233*	1.00	−0.069
ΔTG	0.550**	0.128	−0.175	1.0

* $P < 0.05$, ** $P < 0.01$.

found between the change in HDL-C with training and baseline HDL-C (r = −0.462). The association was even stronger in studies reporting significant increases in HDL-C with training (r = −0.676). This finding is in agreement with that of the HERITAGE Family Study (43); however, a few studies have reported contradictory findings, i.e., that subjects with reduced baseline HDL-C levels were less likely to respond to training (82,86). The only other significant univariate association with increased HDL-C was with a change in LDL-C with training (r = −0.402). No significant associations were observed with weekly energy expenditure during the exercise programs, probably because in almost all of the studies the training volume exceeded the threshold of 3347–4184 $kJ \cdot wk^{-1}$ (800–1,000 $kcal \cdot wk^{-1}$) postulated to be required to raise HDL-C (13,38), or with training intensity, session duration, or length of the training program. Also, no significant associations were observed between change in HDL-C and changes with training in body weight, $\dot{V}O_{2max}$, or with change in TG across studies. However, all lipid parameters generally improved in studies in which there was a substantial weight loss (≥4 kg), usually associated with a concomitant hypocaloric diet. The HERITAGE Family Study (43) also failed to find significant associations between change in HDL-C and change in $\dot{V}O_{2max}$ and body weight with exercise training. Change in TC with training was inversely related to baseline LDL-C levels (r = −0.420), whereas change in TG was associated with baseline levels of body weight (r = 0.435), TG (r = −0.290), and HDL-C (r = 0.348), and with change with training in TC (r = 0.550) (all $P < 0.01$). Stepwise multiple linear regression analyses also were performed on data from intervention studies limited to exercise alone using the percent changes from before to after training in lipid parameters as dependent variables. Independent variables entered included age and sex; baseline levels of BMI, $\dot{V}O_{2max}$, and blood lipids; kilojoules per week of exercise performed; and changes after training in body weight, $\dot{V}O_{2max}$, and blood lipids. The only predictors accepted in the models for changes in HDL-C were baseline HDL-C level and the training-induced change in LDL-C level with the $r^2 = 0.436$ ($P < 0.003$). The corresponding r^2 for the percent change in TC with training was 0.744 with baseline TC and LDL-C and changes with training in LDL-C and TG entering into the model. A similar r^2 was found for the change in LDL-C with baseline TC and LDL-C and changes in TC and HDL-C entering into the model. The r^2 for change in TG was 0.473 with baseline body mass and the changes with training in body mass and TC entering into the model.

DISCUSSION

Evidence evaluation. Does the available evidence support the hypothesis that endurance exercise training has a favorable influence on the blood lipid profile relative to future risk of CHD? Although there is a great deal of inconsistency in the response of blood lipids to endurance exercise training in both RCT and non-RCT, the bulk of the evidence supports this hypothesis. The most frequently observed change is an increase in HDL-C, a protective factor against CHD (Evidence Category B). It is estimated that for every 0.026 $mmol \cdot L^{-1}$ (1 $mg \cdot dL^{-1}$) increase in HDL-C, the risk for a CHD event is reduced by 2% in men and at least 3% in women (51,52). Reduction in TC, LDL-C, and TG also may occur with training (Category B). In general, a 1% reduction in LDL-C is associated with a 2–3% lower risk of CHD (47). Exercise training also appears to attenuate the reduction in HDL-C accompanying a decreased dietary intake of saturated fat and cholesterol to promote reduction of LDL-C.

Does the blood lipid response to training differ by sex, age, race/ethnicity of study subjects, and baseline lipid levels, and baseline body weight and its change with training? Earlier reviewers noted a trend for a lower prevalence of training-induced increase in HDL-C levels in women (13,17,38,69). However, the data reviewed here suggest that sex is not a predictor of responsiveness of HDL-C to training, with adult men and women appearing to respond similarly (Category B). Age also does not appear to be a predictor of lipid responsiveness to exercise training, with elderly men and women as likely, or perhaps even more likely, than younger individuals to increase HDL-C with training (Category B). Only limited data are available on racial and ethnic differences in the response of lipids to exercise training. In the largest supervised exercise training study to date, the HERITAGE Family Study, there were no significant sex, age, or black/white differences in the extent (and variability) of the HDL-C response to training (43). Baseline body weight was found in this review to be inversely related to change in TG (but not to the other lipid variables under consideration). Studies in which a sizable weight loss was obtained while holding the percent of energy intake constant generally had a favorable effect on the entire lipid/lipoprotein profile (Category A); however, a concomitant reduction in percent energy from fat clearly reduces the HDL-C response to exercise. Only a limited number of studies have been performed on people with hypercholesterolemia and/or hypertriglyceridemia. On the basis of this review, baseline lipid levels appear to strongly influence the lipid response to training. A low pretraining

HDL-C was shown to be a moderately strong predictor of a positive HDL-C response to training, whereas baseline LDL-C was inversely associated with posttraining change in TC (Category B).

Is the response of blood lipids to exercise related to the intensity, duration, the weekly volume of energy expenditure; the length of the endurance exercise program; and the associated change in $\dot{V}O_{2max}$? There currently are insufficient data from available training studies to conclusively establish a dose-response relationship between intensity and volume of exercise and lipid responses, suggested by observational studies (13,38,81). There have been only a limited number of studies directly evaluating the effects of different exercise intensities on blood lipids. Most of the studies reviewed here showing HDL-C changes used an exercise prescription involving moderate- to hard-intensity activities for at least 30 min, three times per week can raise HDL-C (Category B evidence for moderate- to hard-intensity exercise). There is limited evidence of additional benefits from higher intensity exercise (Category C). There also is limited evidence that lower intensity (light-intensity) exercise may be as effective as moderate-intensity exercise in raising HDL-C (Category C). No differences were found between HDL-C responders and nonresponders to training in the duration of exercise sessions and weekly volume of exercise performed. This probably was because the weekly volume of exercise used in most of the studies in this survey (a mean of about 6276 kJ (1500 kcal) for men and 5044 kg (1205 kcal) for women) probably exceeded the threshold required to increase HDL-C. In addition, no association was found between length of the training program (>12 wk) and HDL-C response (Category B). It also appears from the studies in Tables 1–3 that prescribed nonstructured or so-called lifestyle activities have little or no impact on the blood lipid profile (Category B). In most of the studies reported here, training resulted in at least a moderate increase in $\dot{V}O_{2max}$, as would be expected, since investigators generally followed ACSM exercise prescription guidelines for improving $\dot{V}O_{2max}$. However, no significant correlation was found between the increase in $\dot{V}O_{2max}$ and change in HDL-C with training (Category A).

Research priorities. There remain many unanswered questions pertaining to the impact of exercise on blood lipids and lipoprotein that require future studies. Subjects for future investigations should include ethnic minorities and people of all ages with dyslipidemia, including those with isolated low HDL-C levels, since there is currently a paucity of data from such populations. Recommended study topics should include:

1. Large-scale, multicenter RCT to better define the dose-response relationships of progressively higher weekly volumes of energy expenditure via light-, moderate-, and hard-intensity exercise on blood lipid responses for periods up to 1 yr, with repeated lipid measurements during training to determine the relationship of duration of training to the observed lipid changes (e.g., measurements at 3, 6, 9, and 12 mo).
2. Investigations to determine how long exercise-induced changes persist during "detraining," and to define the minimal or optimal volume of exercise to maintain exercise-induced lipid changes.
3. Investigations to better elucidate true training-induced blood lipid adaptations from transient (acute) effects of the most recent training session (e.g., by performing blood lipid assays adjusted for plasma volume changes at 12, 24, 48, and 72 h after the last training session).
4. Additional metabolic studies to better define mechanisms for blood lipid changes with exercise training.
5. Further investigations on the contribution of site-specific reductions in adipose tissue mass to blood lipid response to training.
6. Molecular biological investigations to identify genetic markers for HDL-C responders and nonresponders to exercise training.
7. Studies to further investigate the interactions of simultaneous dietary interventions and exercise training on blood lipids in patients with dyslipidemias with attempts to modify the diet plan so as to achieve optimal LDL-C reduction without adversely affecting the HDL-C (and TG) response to exercise.
8. Investigation of the interactions of cholesterol-lowering medications (particularly the HMG-coenzyme A reductase inhibitors or "statin" drugs) and exercise programs on blood lipids.

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Dose-response and coagulation and hemostatic factors

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ABSTRACT

RAURAMAA, R., G. LI, and S. B. VÄISÄNEN. Dose-response and coagulation and hemostatic factors. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S516–S520. **Purpose:** The purpose of this study was to evaluate the dose-response relations of regular physical activity on platelet function, blood coagulation factors, and fibrinolytic factors, on the basis of studies with appropriate experimental design. **Methods:** MEDLINE-based literature search supplemented with relevant review articles and other individual articles was used. The review concentrates on controlled randomized clinical trials on the impact of regular physical exercise on platelet function, and on blood coagulation and fibrinolytic factors. **Results:** Physical exercise acutely activates platelets and the fibrinolytic system, and some factors of the blood coagulation cascade. These findings, the earliest of which were published already in the 1960s, are mainly derived from uncontrolled observations. These studies have led to the conclusion that unbalanced activation of the hemostatic system during acute exercise may be part of the mechanisms for sudden cardiac events during or shortly after heavy physical exercise. The effects of regular physical exercise on various aspects of platelet function, blood coagulation, and fibrinolysis have been the object in only a few controlled randomized trials. With the exception of data on platelet function, the results remain contradictory. **Conclusion:** Controlled randomized clinical trials with adequate statistical power and experimental study designs with subjects of different ages and health status are warranted for the evaluation of the dose-response issues to clearly delineate the preventive and therapeutic potential of regular physical exercise. **Key Words:** EXERCISE TRAINING, CONTROLLED RANDOMIZED CLINICAL TRIAL, PLATELET FUNCTION, BLOOD COAGULATION, FIBRINOLYSIS

Cardiovascular diseases remain a major public health concern in Western societies, despite the favorable trends in mortality and morbidity during the last three decades. Thrombosis is a key event in the pathophysiology of acute cardiovascular complications such as myocardial infarction and stroke. Although the many beneficial effects of regular physical exercise on blood lipids and blood pressure have been quite well documented, systematic research focusing on thrombogenesis has gained much less attention. This review is derived from controlled randomized trials on the effects of regular exercise training on various aspects of hemostasis, a complicated system characterized by delicate positive and negative feedback regulations. Even if data published from uncontrolled studies seem to fit perfectly with general expectations on health-enhancing effects of regular physical activity, it is unlikely that negative results from uncontrolled studies get published in respected journals. Therefore, to avoid biased impression, any conclusions regarding the effects of physical exercise on blood hemostatic system should be determined on the basis of controlled randomized design. Even if this basic requirement is fulfilled, experimental protocols require extremely careful standardization. Currently, data available on dose-response issues on physical exercise and blood hemostasis are limited.

Table 1 shows the published controlled randomized clinical trials on the effects of regular physical exercise on platelet function, blood coagulation, and fibrinolytic factors. Evidently, every study provides only fragmentary data on hemostatic changes attributable to physical exercise. This hampers a comprehensive evaluation of the potential that regular physical exercise may have. Perhaps one major contributor for the paucity of data might be lack of sufficient funding to carry out a comprehensive study, and not necessarily the lack of ideas for hypotheses to be tested.

CURRENT STATUS OF KNOWLEDGE

Platelet Function

Acute effects of physical exercise on platelet function have been reported from several studies (4,5) but with contradictory results, most likely because of methodological problems in monitoring platelet activation state during or immediately after physical exercise. Two recent studies have overcome the methodological shortcomings. Strenuous physical exercise activates platelets in sedentary, but not in physically active, healthy subjects, as elegantly demonstrated by using monoclonal antibodies directed against several platelet surface receptors (13). This effect may be

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TABLE 1. Summary table of controlled randomized trials on the effects of aerobic exercise training on platelet function, blood coagulation, and fibrinolysis in the resting state.

	Study Subjects				Exercise Program		Outcome Measures		
References	*N*	Sex	Age Range (yr)	Clinical Status	Duration (mo)	Intensity	Platelet Function	Coagulation	Fibrinolysis
Rauramaa et al., 1984 (22)	60	M	32–44	H	2	Mod	PGI_2: increased		
Rauramaa et al., 1986 (23)	59	M	35–49	O	3	Mod	AGGR: decreased		
Wosornu et al., 1992 (45)	55	M	32–70	P	6	Mod to hard		FBG: decreased FVII: increased	
Rankinen et al., 1994 (20)	119	M	51–53	H	6	Mod		FBG, FVII, FX, AT-III: unchanged	PAI-1, t-PA: unchanged
Anderssen et al., 1995 (1)	219	M, F	40	S	12	Hard	β-ThrGLB: unchanged	FBG, FVII: unchanged	PAI-1, t-PA: unchanged
El-Sayed et al., 1995 (5)	25	M, F	32–33		3	Hard		FBG: unchanged	
Wang et al., 1995 (40)	23	M	20–22	H	2	Mod	AGGR: decreased ADHES: decreased		
Svendsen et al., 1996 (32)	121	F	50–56	O	3	Hard		FBG: unchanged	PAI-1, t-PA: unchanged
Schuit et al., 1997 (31)	229	M, F	60–80	H	6	Hard		FBG: increased	PAI-1: decreased t-PA: increased
Wang et al., 1997 (41)	16	F	20–25	H	2	Mod	AGGR: decreased ADHES: decreased		
Tisi et al., 1997 (35)	82	M, F	66–69	C	12	Hard		FBG: unchanged	PAI-1: unchanged
van den Burg et al., 1997 (36)	39	M	20–30	H	3	Hard		FVII, FVIII, FIX, FXII, FBG: unchanged	t-PA: unchanged
Väisänen et al., 1999 (38)	136	M	53–63	H	36	Mod			PAI-1: decreased in the 4G4G subjects
Rauramaa et al., 2000 (25)	125	M	53–63	H	36	Mod		FBG: unchanged	

AGGR, platelet aggregability; ADHES, platelet adhesion; β-ThrGLB, β-thromboglobulin; PGI_2, prostacyclin; FBG, fibrinogen; FVII, factor VII; FX, factor X; AT-III, antithrombin III; PAI-1, plasminogen activator inhibitor type 1; t-PA, tissue plasminogen activator; Mod, moderate; Clinical status codes: C, claudication patients; H, healthy; HC; healthy, CVD patients; O, overweight; P, Postbypass surgery; S, sedentary, high CVD risk.

because of the higher catecholamine response during exercise in sedentary subjects compared with habitually active subjects. Although strenuous physical exercise in young healthy subjects increases platelet adhesion and aggregation in sedentary as well as in physically active subjects, moderate exercise at the level of 50–55% of peak oxygen consumption apparently has an inhibitory effect, at least in sedentary subjects (42).

In contrast to reports on the acute effects of physical exercise, only a few data are available on regular exercise training and platelet function. As shown in Table 1, three controlled randomized trials have been aimed at platelet function (23,40,41). In addition, two other controlled randomized trials are relevant with regard to regular exercise training and platelet function. An earlier study reported on the prostacyclin-increasing effect of regular physical exercise in healthy middle-aged men (22). Recently, another study reported improved endothelial function in patients with coronary artery disease after a high-intensity exercise training program (8).

In their methodologically exemplary studies, Wang et al. (40,41) showed that regular physical exercise of moderate intensity in young healthy men and women decreases platelet adhesive and aggregative properties both at rest and after acute strenuous exercise. Another important finding was that a period of deconditioning reverses the resting and exercise-induced beneficial effects on platelet function back to the pretraining level (40,41). In an earlier study in overweight, mildly hypertensive middle-aged men, low- to moderate-intensity regular physical activity reduced platelet aggregability (23).

Increased serum high-density lipoprotein (HDL) cholesterol, a well known consequence of regular exercise training, was found to be associated with increased plasma prostacyclin, a potent inhibitor of platelet aggregation. Regular exercise training increases release of nitric oxide, which carries potent antiplatelet effects by stimulating platelet guanylate cyclase with ensuing elevation of cyclic guanosine monophosphate contents in platelets, and this in turn suppresses platelet reactivity (41).

The three studies cited, even if carried out following an appropriate study design, do not justify Evidence Category A for the dose-response issues of physical exercise on platelet function. Therefore, more studies are clearly needed in order to conclude more precisely the dose-response relations of regular physical exercise on platelet function, at rest as well as during physical exercise.

Evidence statement. Regular physical exercise of low to moderate intensity has an inhibitory effect on platelet adhesion and aggregation at rest or during physical exercise. Evidence Category B.

Blood Coagulation Factors

Fibrinogen. Epidemiological studies show that increased fibrinogen level is an independent risk factor for cardiovascular disease and mortality (12,17,44). Even if it has not been demonstrated that lowering of plasma

fibrinogen level results in reduction in cardiovascular morbidity and mortality, it can be deducted from the strong epidemiological evidence. Fibrinogen promotes platelet aggregation, plays a central role in the final phase of the blood coagulation cascade, and is a key determinant of blood viscosity. Fibrinogen is elevated in inflammatory states, smokers, obesity, diabetes, and hyperlipidemias. Fibrinogen is an acute phase protein, and it has a relatively high intraindividual variability (26,39). Therefore, repeated measurements and large enough sample sizes are prerequisites to reveal any intervention effects on plasma fibrinogen level (26).

Although the pharmacological tools to reduce plasma fibrinogen level are limited, the possible significance of regular physical exercise has gained increasing attention. Indeed, an inverse relationship between fibrinogen and physical activity and/or cardiorespiratory fitness has been consistently found in cross-sectional studies (37). However, the fibrinogen-lowering effect of regular physical activity remains to be explored in additional controlled randomized trials. Currently, data are available from nine controlled randomized clinical trials. Six studies were at least of 6 months' duration and included a reasonable number of subjects; one study reported a decrease, one an increase, and four no changes in plasma fibrinogen level (Table 1).

There could be several methodological explanations for the discrepant results. Differences in study protocols, particularly in the timing of blood sampling after last bout of exercise, may be one explanation. As the half-life of fibrinogen is 3–4 d, it may well be that in some studies the plasma fibrinogen measurement represents the acute phase reaction, whereas in other studies too much time has elapsed between last exercise bout and blood sampling. Recently, three studies have examined whether genetic polymorphisms in the fibrinogen genes can modulate the association between physical activity and plasma fibrinogen, which may partly explain contradictory results.

An acute phase response in fibrinogen level was reported in young men after an exhausting 2-d military exercise period. The subjects carrying the A allele of the G-453-A polymorphism in the β-fibrinogen gene had a higher increase in plasma fibrinogen than did men with the GG genotype (18). In postmenopausal women, an interaction was found between habitual physical activity and an α-fibrinogen gene polymorphism on fibrinogen level. The physically most active women, who were homozygous for the more frequent *Rsa I* allele (Thr/Thr genotype), displayed a decreased plasma fibrinogen, whereas the association was not seen in other genotypes (24). In our ongoing controlled randomized trial, the DNASCO study, we did not find any statistically significant differences between exercise and reference groups in plasma fibrinogen level, after 3 yr of exercise intervention. Instead, there was an inverse association between the changes in submaximal performance capacity and plasma fibrinogen level in the exercise group in the Thr/Thr men (25).

Additional controlled randomized exercise intervention trials are needed to further evaluate the relationship between physical activity and fibrinogen level. Evidently, such studies would benefit from inclusion of genetic polymorphisms into the analyses, preferably already at the randomization phase.

Other coagulation factors. As shown in Table 1, there is an obvious need for controlled randomized trials on the effects of physical exercise training on other coagulation factors.

Blood fibrinolytic factors. Elevated plasminogen activator inhibitor type 1 (PAI-1) activity, a common finding in the obese, in diabetic subjects, as well as in subjects with metabolic syndrome, increases the risk of cardiovascular disorders (9,11,27). More specifically, the 4G allele of the 4G/5G polymorphism in the PAI-1 promoter gene associates with an increased PAI-1 level and higher risk of cardiovascular diseases (6,16,19). Several preanalytical factors such as diurnal variation and difficulties in blood collection and handling have significant effects on fibrinolytic activity (10,14), and these confounding factors make it essential to include a reference group in a study design.

The acute response of the fibrinolytic system to physical exercise has been the object in several cross-sectional type trials, typically comparing physically active versus sedentary subjects, or simply comparing athletes before and after strenuous exercise. A common conclusion from several reviews is that physical exercise acutely stimulates fibrinolytic activity, in concert with the increase in blood coagulation.

Tissue-plasminogen activator (t-PA) and PAI-1 are the two fibrinolytic components the activities of which can be specifically measured. Moderate-intensity physical exercise increases acutely t-PA activity, with higher increases at strenuous and maximal exercise (21,34). On the other hand, PAI-1 activity remains unchanged at moderate intensity, but decreases at strenuous and maximal levels (20,34). Fibrinolytic activity both at rest, after submaximal (3), or after maximal physical exercise (7) is similar in physically active men with or without a history of myocardial infarction (7) as well as in older men with hypertension compared with normotensive subjects (3). The changes in both t-PA and PAI-1 activities appear to be more marked during exercise performed in the evening compared with exercise taken in the morning (33), and they return to preexercise levels within 24 h (21). Increased plasma epinephrine during exercise is the primary stimulus for t-PA, thereby leading to reduction in PAI-1 activity (2).

The impact of regular physical exercise on blood fibrinolytic activity has been studied in six controlled randomized trials. Except for one trial applying strenuous exercise, t-PA and PAI-1 activities have remained unchanged (Table 1). However, in a study by Väisänen et al. (38), low to moderate regular physical exercise during 3 yr decreased PAI-1 activity in the exercise group in those men homozygous for the 4G allele.

The active role of adipose tissue as an important contributor to thrombogenesis has been understood only very recently (29). Elevated plasma PAI-1 activity may result in PAI-1 release from an increased visceral adipose tissue (15). In addition to insulin (28), two cytokines, tumor necrosis

factor-α (TNF-α) and transforming growth factor-β (TGF-β), induce PAI-1 gene expression in the adipose tissue, the excess of which in obese subjects serves as an additional source for PAI-1 production (28,30). Strenuous physical activity in young athletes increases acutely serum TNF-α (43). However, it is not known how regular exercise training may modulate these two cytokines chronically or acutely in response to a single bout of physical exercise.

RESEARCH ISSUES

A basic requirement in future studies on the topic should be a controlled randomized trial with appropriate sample size. With such study design the risk for erroneous conclusions will be minimized. Furthermore, the preventive and therapeutic utility of regular exercise will be more rational. We suggest the following research topics for future clinical trials for the purpose of establishing a scientific basis for exercise prescription:

1. Effects of regular low- (40–50% of $\dot{V}O_{2max}$) to moderate-intensity (50–60% of $\dot{V}O_{2max}$) aerobic physical activity and/or muscular strength training on platelet function, blood coagulation, and fibrinolytic factors at rest, during physical exercise, and during the recovery phase in order to find out the duration of the exercise-induced effects. These trials should be targeted at least the following: healthy, asymptomatic subjects of both genders and various ages, obese subjects, subjects with impaired glucose tolerance and/or type 2 diabetes, subjects with metabolic syndrome, subjects with atherosclerotic cardiovascular diseases, and postmenopausal women.
2. Role of genetic polymorphisms in hemostatic factors in response to regular physical activity of different intensities, exercise modalities, and subjects, as outlined above, on platelet function, blood coagulation, and fibrinolytic factors.

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Physical activity, total and regional obesity: dose-response considerations

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ABSTRACT

ROSS, R., and I. JANSSEN. Physical activity, total and regional obesity: dose-response considerations. *Med. Sci. Sports Exerc.,* Vol. 33, No. 6, Suppl., 2001, pp. S521–S527. **Purpose:** This review was undertaken to determine whether exercise-induced weight loss was associated with corresponding reductions in total, abdominal, and visceral fat in a dose-response manner. **Methods:** A literature search (MEDLINE, 1966–2000) was performed using appropriate keywords to identify studies that consider the influence of exercise-induced weight loss on total and/or abdominal fat. The reference lists of those studies identified were cross-referenced for additional studies. **Results:** *Total fat.* Review of available evidence suggested that studies evaluating the utility of physical activity as a means of obesity reduction could be subdivided into two categories based on study duration. Short-term studies ($\leq$16 wk, N = 20) were characterized by exercise programs that increased energy expenditure by values double (2200 vs 1100 kcal·wk^{-1}) that of long-term studies ($\geq$26 wk, N = 11). Accordingly, short-term studies report reductions in body weight (-0.18 vs -0.06 kg·wk^{-1}) and total fat (-0.21 vs -0.06 kg·wk^{-1}) that are threefold higher than those reported in long-term studies. Moreover, with respect to dose-response issues, the evidence from short-term studies suggest that exercise-induced weight loss is positively related to reductions in total fat in a dose-response manner. No such relationship was observed when the results from long-term studies were examined. *Abdominal fat.* Limited evidence suggests that exercise-induced weight loss is associated with reductions in abdominal obesity as measured by waist circumference or imaging methods; however, at present there is insufficient evidence to determine a dose-response relationship between physical activity, and abdominal or visceral fat. **Conclusion:** In response to well-controlled, short-term trials, increasing physical activity expressed as energy expended per week is positively related to reductions in total adiposity in a dose-response manner. Although physical activity is associated with reduction in abdominal and visceral fat, there is insufficient evidence to determine a dose-response relationship. **Key Words:** PHYSICAL ACTIVITY, OBESITY, ABDOMINAL FAT, VISCERAL FAT, WEIGHT LOSS, DOSE-RESPONSE

It is generally accepted that a decrease in daily physical activity has contributed to the increased prevalence of obesity worldwide (13,18,31,47). Accordingly, limited evidence also suggests that an increase in physical activity (exercise) without caloric restriction is a useful strategy for reducing obesity, in particular, abdominal and visceral obesity (38,39,40,44). This review was undertaken to determine whether exercise-induced weight loss is associated with corresponding reductions in total, abdominal, and visceral fat in a dose-response manner.

The format of this review follows the guidelines set forth in the recent National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI) document (31). As such, Section A (Current Knowledge) consists of a series of Evidence Statements followed by a brief rationale. Following each Evidence Statement is an Evidence Category that is generally consistent with the criteria established by the Expert Panel (31).

To consider the influence of varying levels of physical activity on total and abdominal obesity, a MEDLINE search (1966–2000) was performed using "weight loss" and "exercise" as keywords. The reference lists of those studies identified were then reviewed for additional studies. Appropriate studies were identified using the following inclusion criteria:

1. The subjects participating in the exercise group either had to consume an isocaloric diet for the duration of the study, thereby ensuring that the negative energy balance observed (e.g., significant reduction in total and/or abdominal fat) was induced by the increase in physical activity or the subjects in the physical activity (exercise) group were instructed not to change their diet (eating) habits and thus, in theory, a negative energy balance would be induced by an increase in exercise.
2. The subjects were overweight or obese, and thus the mean BMI values had to be greater than 25.0 kg·m^{-2} (31). For studies not reporting BMI values, the mean percent body fat had to be greater than 20% in men and greater than 33% in women, values that correspond to a BMI of 25.0 kg·m^{-2} (15).
3. That measurements of whole-body or abdominal fat were obtained using established methods (e.g., underwater weighing, duel energy x-ray absorptiometry, computed tomographic scan, magnetic resonance imaging (MRI), and waist circumference).
4. That the authors reported the caloric expenditure of the exercise or provided the information required to permit estimation of oxygen cost and caloric expenditure

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(e.g., $\dot{V}O_{2max}$, exercise frequency, intensity, and duration).

CURRENT STATUS OF KNOWLEDGE

Evidence statement. Physical activity is associated with reductions in total fat in a dose-response manner within trials that are less than 4 months in duration (Evidence Category B).

Nine randomized, controlled trials (RCT) (Table 1) and 22 nonrandomized trials (Table 2) met the inclusion criteria. Before considering the relationship between varying levels of physical activity and obesity reduction, we examined the findings of all studies with respect to the utility of exercise to induce fat loss. In so doing, it was noted that the findings differed substantially depending on the duration of the study. Indeed, short-term RCT (≤16 wk, $N = 5$) are characterized by relatively high energy expenditures (~2200 kcal·wk^{-1}) that correspond to an average weight loss of 0.26 kg·wk^{-1} and fat loss of 0.25 kg·wk^{-1} (Table 1). By comparison, long-term RCT (≥26 wk, $N = 4$) are characterized by energy expenditures of about 1100 kcal·wk^{-1} that correspond to an average 0.06 kg·wk^{-1} reduction in both body weight and total fat. A similar pattern of observations was noted for the nonrandomized studies (Table 2). Short-term exercise studies ($N = 15$) generally report much greater reductions in body weight (−0.18 vs −0.06 kg·wk^{-1}) and total fat (−0.21 vs −0.06 kg·wk^{-1}) by comparison with long-term studies ($N = 7$). In addition, study duration (short-term vs long-term) also influenced the relationships observed between varying levels of physical activity and obesity reduction (e.g., dose-response).

To determine whether physical activity (exercise) was associated with reduction in total fat in a dose-response manner, we regressed the average weekly energy expenditure values (e.g., group means obtained from each study) with the corresponding reductions in total fat. For short-term studies (RCT and nonrandomized combined, $N = 20$), the reduction in total adiposity was positively related to energy expenditure (Fig. 1). In other words, the greater the energy expended by exercise, the greater the fat loss. No relationship was observed when the average increase in physical activity was regressed with the average reduction in total fat for the long-term studies (RCT and nonrandomized combined ($N = 12$), Fig. 1). In addition, independent of the magnitude of the exercise-induced energy deficit, for both RCT and nonrandomized studies combined, the reduction in body weight achieved within the short-term studies approached 85% of that expected (Fig. 1). This contrasts with observations in long-term studies wherein the achieved weight loss was about 30% of that expected.

From the studies in Tables 1 and 2 come the following summary observations:

1. Results from short-term (≤16 wk) studies reveal that an increase in physical activity is positively associated with a reduction in total fat in a dose-response manner. This is not the case for long-term (≥26 wk) studies.
2. Only three studies prescribed exercise for women of a magnitude greater than ~1500 kcal·wk^{-1}; thus, the dose-response relationship is determined in large measure on the basis of findings from studies using male subjects.
3. On average, the weight loss attained in short-term studies is approximately 85% of that expected, and is composed almost entirely of fat.
4. The influence of age, race, and gender on these observations is unknown.

TABLE 1. Influence of caloric expenditure on changes in body weight and total body fat: evidence from randomized, controlled trials.

	Subjects									
		BMI			Study	Energy	Exercise	Expected	Actual Δ	Actual Δ
Reference	Sex	kg·m^{-2}	% Fat	Treatment	Duration (wk)	Expenditure (kcal·wk^{-1})	Duration (min·wk^{-1})	Weight Loss (kg·wk^{-1})[b]	Weight (kg·wk^{-1})	Body Fat (kg·wk^{-1})
Studies ≤16 wk duration										
Posner et al., 1992	81 older adults		28	Control	16	—	—	—	−0.01	0.02
(35)[a]	166 older adults		28	Exercise		490	90	−0.06	0.03	−0.03[c]
Maurier et al., 1997	11 diabetics	30		Control	8	—	—	—	−0.02	−0.15
(30)[a]	10 diabetics	30		Exercise		840	112	−0.11	−0.19	−0.07
Hinkleman and Neiman,	18 women		34	Control	15	—	—	—	0.11	0.06
1993 (22)[a]	18 women		36	Exercise		965	225	−0.13	0.00[c]	−0.01[c]
Sopko et al., 1985 (44)	6 men		28	Control	12	—	—	—	NS	NS
	6 men		31	Exercise		3500	300	−0.46	−0.52[c]	−0.64[c]
Ross et al., 2000 (38)	8 men	31		Control	12	—	—	—	0.01	−0.6
	16 men	32		Exercise		4900	455	−0.63	−0.63[c]	−0.51[c]
Studies ≥26 wk duration										
Kohrt et al., 1997 (25)	12 postmenopausal women	27		Control	39	—	—	—	0.01	0.01
	14 postmenopausal women	27		Exercise		735	147	−0.09	−0.07[c]	−0.08[c]
Binder et al., 1996 (2)[a]	17 older women	25		Control	48	—	—	—	0.01	0.01
	23 older women	25		Exercise		980	140	−0.13	−0.02[c]	−0.05[c]
Wood et al., 1988 (48)[a]	42 men		29	Control	52	—	—	—	0.00	−0.01
	47 men		27	Exercise		1330	133	−0.17	−0.08[c]	−0.08[c]
Ready et al., 1995 (36)	10 postmenopausal women	32		Control	26	—	—	—	0.02	0.01
	15 postmenopausal women	29		Exercise		1500	266	−0.20	−0.07[c]	−0.05[c]

NS, nonsignificant change.

[a] The exercise energy expenditure was not reported. The oxygen cost was estimated on the basis of the subjects' $\dot{V}O_{2max}$, exercise intensity, frequency, and duration. Energy expenditure was subsequently determined by multiplying the oxygen cost by 5 kcal·L^{-1}.

[b] Expected change in weight on the basis of weekly caloric expenditure. It was assumed that 7700 kcal = 1 kg.

[c] Reduction in exercise group significantly greater than reduction in control group ($P < 0.05$).

TABLE 2. Influence of caloric expenditure on changes in body weight and total body fat: evidence from nonrandomized trials.

Reference	Subjects: Sex	Subjects: BMI kg·m^{-2}	Subjects: BMI % Fat	Treatment	Study Duration (wk)	Energy Expenditure (kcal·wk^{-1})	Exercise Duration (min·wk^{-1})	Expected Weight Loss (kg·wk^{-1})[b]	Actual Δ Weight (kg·wk^{-1})	Actual Δ Body Fat (kg·wk^{-1})
Studies ≤16 wk duration										
Poehlman et al., 1994 (33)[a]	18 older adults	25		Exercise	8	665	154	−0.09	0	−0.05
Goran and Poehlman, 1992 (19)[a]	11 older adults		30	Exercise	8	665	91	−0.09	0	−0.11[d]
Weltman et al., 1980 (46)[a]	5 men		28	Control	10	—	—	—	−0.03	0.02
	11 men		23	Exercise		770	182	−0.1	−0.10	−0.10[c]
Reid et al., 1994 (37)[a]	7 adults	30		Exercise	12	945	119	−0.12	−0.04	−0.09
Grediagin et al., 1995 (17)	6 women	24		HI Ex	12	1190	140	−0.16	−0.06	−0.19
	6 women	26		LI Ex		1190	224	−0.16	−0.27[d]	−0.19
Gordon et al., 1997 (16)[a]	14 hypertensive adults	34		Exercise	12	1365	147	−0.17	−0.08	−0.07
Farrell and Barboriak, 1980 (12)[a]	7 men	28		Exercise	8	1505	105	−0.20	−0.25	−0.21[d]
	9 women	24		Exercise		840	105	−0.11	−0.06	−0.11[d]
Houmard et al., 1994 (23)[a]	13 men	30		Exercise	14	1505	154	−0.2	−0.14[d]	−0.20[d]
Kollias et al., 1973 (27)	5 young women	30		Exercise	15	1610	245	−0.21	−0.38[d]	−0.22[d]
Schwartz, 1987 (41)[a]	14 obese men		31	Exercise	12	1715	119	−0.22	−0.23[d]	−0.29[d]
Hagan et al., 1986 (21)[a]	12 men		25	Exercise	12	1785	147	−0.23	−0.02	−0.02
	12 women		35	Exercise		1130	147	−0.15	−0.05	−0.12
Keim et al., 1990 (24)[a]	5 women		35	Exercise	12	2380	245	−0.31	−0.42[d]	−0.37[d]
Boileau et al., 1971 (3)	8 young men	37		Exercise	9	2765	300	−0.36	−0.36[d]	−0.66[d]
Bouchard et al., 1994 (5)	14 young men		24	Exercise	13	4375	357	−0.57	−0.38[d]	−0.38[d]
Leon et al., 1979 (29)	6 young men	33		Exercise	16	5495	448	−0.71	−0.47[d]	−0.37[d]
Studies ≥20 wk duration										
Smutok et al., 1993 (43)[a]	10 men	29		Control	20	—	—	—	0.04	0.01
	13 men	28		Exercise		945	91	−0.12	−0.02	−0.07
Poirier et al., 1996 (34)[a]	11 diabetic men		27	Exercise	26	1225	154	−0.16	−0.03	−0.02
Frey-Hewitt et al., 1990 (14)[a]	44 men		27	Exercise	46	1470	182	−0.19	−0.09	−0.09[d]
Coggan et al., 1992 (6)[a]	12 older men		28	Exercise	43	1505	175	−0.20	−0.08[d]	−0.08[d]
	11 older women		36	Exercise		1505	175	−0.20	−0.05[d]	−0.06[d]
Kohrt et al., 1992 (26)	16 older men	25		Control	~45	—	—	—	0.00	−0.01
	47 older men	27		Exercise		1890	182	−0.24	−0.12[c]	−0.06[c]
	13 older women	24		Control		—	—	—	0.03	0.02
	46 older women	25		Exercise		1120	182	−0.14	−0.04[c]	−0.04[c]
Després et al., 1991 (8)[a]	13 women	34		Exercise	60	2450	406	−0.32	−0.06[d]	−0.08[d]
Lamarche et al., 1992 (28)[a]	31 women	34		Exercise	26	2450	406	−0.32	−0.03	−0.03

HI Ex, high-intensity exercise; LI Ex, low-intensity exercise.
[a] The exercise energy expenditure was not reported. The oxygen cost was estimated on the basis of the subjects' $\dot{V}O_{2max}$, exercise intensity, frequency, and duration. Energy expenditure was subsequently determined by multiplying the oxygen cost by 5 kcal·L^{-1}.
[b] Expected change in weight on the basis of weekly caloric expenditure and duration of study. It was assumed that 7700 kcal = 1 kg.
[c] Reduction in exercise group significantly greater than reduction in control group ($P < 0.05$).
[d] Significant within-group reduction ($P < 0.05$).

Evidence statement. There is insufficient evidence to determine whether an increase in physical activity is associated with a corresponding reduction in abdominal obesity in a dose-response manner (Evidence Category C).

Four RCT considered the effects of exercise on abdominal obesity measured using waist circumference (Table 3). From these studies it is difficult, if not impossible, to determine the influence of varying levels of physical activity on abdominal fat. Indeed, within two studies the reduction in waist circumference in the exercise group was not significant by comparison with controls (Table 3). Moreover, with the exception of Ross et al.(38), all other studies that considered the influence of physical activity on abdominal fat are characterized by relatively low levels of physical activity (840–1890 kcal·wk^{-1}). Evidence from nonrandomized studies reinforce the observation that varying levels of physical activity, expressed as energy expended per week, are not related to concurrent reductions in waist circumference (Table 3).

Only three RCT and three nonrandomized studies meeting the inclusion criteria report whether physical activity is associated with reductions in visceral fat (Table 3). From

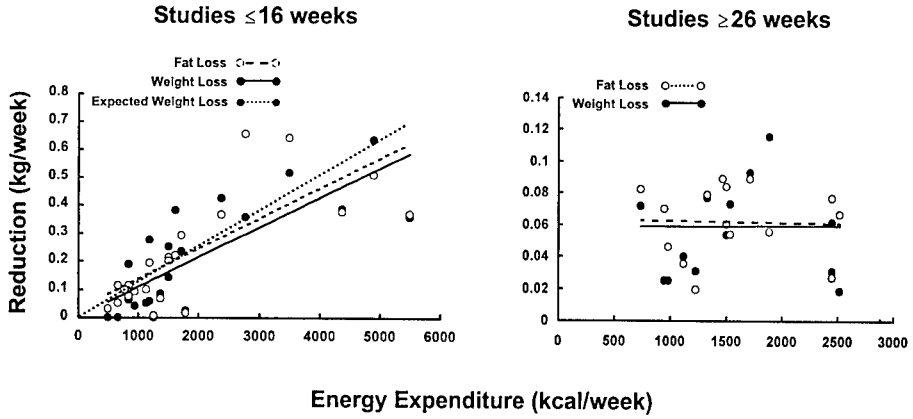


FIGURE 1—Illustration of the relationship between energy expenditure expressed as kcal per week, fat loss, weight loss, and expected weight loss expressed in kilograms lost per week. Studies with a duration of 16 wk or less are shown in the left panel, whereas the relationships for studies 26 wk or longer are shown in the right panel.

these studies, although it is generally reported that physical activity is associated with reductions in visceral fat, it is not possible to establish a dose-response relationship. The latter observation may be explained in part by the relatively low levels of visceral fat before treatment for several of the studies reviewed. For example, in three of the four studies that report only minor reduction in visceral fat in response to exercise (8,11,42; young men), initial visceral fat values were, in general, low by comparison with those studies that observed substantial reductions in visceral fat. Whether a threshold exists below which the mobilization of visceral fat in response is markedly reduced, is unknown.

From the studies in Table 3 come the following summary observations:

1) limited evidence suggests that an increase in physical activity is not related to a corresponding reduction in abdominal obesity as measured by either waist circumference or imaging methods in a dose-response manner; and

2) although physical activity is associated with reductions in visceral fat, there is insufficient evidence to establish a dose-response relationship.

Does an Increase in Physical Activity Prevent Weight Gain in a Dose-Response Manner?

A detailed consideration of the role of physical activity in the prevention of weight gain is beyond the scope of this review. However, the role that physical activity plays in attenuating the normal age-related weight gain has recently been reviewed by DiPietro (9) and those interested in this important topic are encouraged to review this work. Within the context of this review, a notable study is that of DiPietro and colleagues (10), who examined the association between changes in body weight and cardiorespiratory fitness (determined by treadmill test) over an average of 7.5 yr in 4599 men. The authors observed a dose-response relationship between change in treadmill time (e.g., change in cardiorespiratory fitness) and body weight. Whereas men who decreased treadmill time (decrease in fitness) gained over 2 kg of body weight, the men without change in treadmill time (maintained fitness) had an increase in body weight of 0.6 kg, whereas the men who increased treadmill time by 1 min (increased fitness) had no change in body weight, and the men who increased treadmill time by 3 min actually decreased body weight by 1.2 kg (10). To interpret a dose-response relationship between physical activity and the prevention of weight gain from the data of DiPietro and colleagues (10), one assumes that the observed increase in treadmill time (fitness) is a consequence of an increase in physical activity. In support of this assumption is the observation that cardiovascular fitness is determined in large measure by physical activity patterns, with heritability accounting for about 25% of the variance in maximal aerobic power (4). To our knowledge, there are no longitudinal studies that report whether physical activity can attenuate the normal increase in total and abdominal fat that occurs with advancing age.

RESEARCH PRIORITIES

Absent from the literature are studies that systematically consider the influence of various levels of physical activity on the reduction of total or abdominal obesity. As a consequence, our consideration of whether a dose-response relationship existed between physical activity and obesity reduction required that we perform a regression analysis inherent to which were several assumptions. First, because the majority of studies reviewed required that we estimate energy expenditure on the basis of mean values for $\dot{V}O_{2max}$, exercise intensity, duration, and frequency (Tables 1 and 2), our regression analysis was dependent on estimates of exercise-induced energy expenditure. Second, although the average exercise-induced energy expenditure values in the studies examined ranged from 500 to 5500 kcal·wk^{-1}, in 75% of the studies energy expended by exercise fell below 1800 kcal·wk^{-1} (Fig. 1 and Tables 1 to 3). Finally, unlike a meta-analysis, we made no attempt to weigh the studies on the basis of, for example, the number of participants in each study. Together, these limitations suggest that the dose-response relationship observed between exercise and obesity reduction be interpreted with caution.

The conclusions of this review are derived in large measure from studies that use middle-aged male, Caucasian subjects; as such, the influence of age and race is unknown. With respect to gender, although 19 of the 31 studies incorporated female subjects, inspection of Tables

TABLE 3. Influence of aerobic exercise on changes in abdominal fat: evidence from randomized, controlled trials and nonrandomized trials.

Reference	Subjects: Sex	Subjects: BMI ($kg \cdot m^{-2}$)	Subjects: % Fat	Treatment	Study Duration (wk)	Energy Expenditure ($kcal \cdot wk^{-1}$)	Exercise Duration ($min \cdot wk^{-1}$)	Δ Waist Girth ($mm \cdot wk^{-1}$)	Δ VAT ($cm^2 \cdot wk^{-1}$) [$\% \cdot wk^{-1}$]	Δ ASAT ($cm^2 \cdot wk^{-1}$) [$\% \cdot wk^{-1}$]	Δ TAAT ($cm^2 \cdot wk^{-1}$) [$\% \cdot wk^{-1}$]
Randomized, Controlled Trials											
Maurier et al., 1997 (30)[a]	11 diabetics	30		Control	8	—	—	0.0	−0.5 [0.4]	−1.1 [0.4]	−1.7 [0.4]
	10 diabetics	30		Exercise		840	112	−1.25	−9.5 [6.1][b]	−5.1 [2.2][b]	−14.5 [3.8]
DiPietro et al., 1998 (11)[a]	7 older adults	27		Control	16	—	—	−1.37	−0.5 [0.6]	+0.7 [0.4]	+0.1 [0.0]
	9 older adults	27		Exercise		910	175	−1.94	−2.0 [0.8]	+1.2 [0.5]	+0.1 [0.0]
Binder et al., 1996 (2)[a]	17 older women	25		Control	48	—	—	0.08	NR	NR	NR
	23 older women	25		Exercise		980	140	−0.60[b]			
Ross et al., 2000 (38)	8 men	31		Control	12	—	—	−0.08	0 [0]	[0.2]	[0.1]
	16 men	32		Exercise		4900	455	−5.42[b]	−4.3 [2.3][b]	[1.5][b]	[1.9][b]
Nonrandomized Trials											
Grediagin et al., 1995 (17)	6 women	24		HI Ex	12	1190	140	~−2.5[c]	NR	NR	NR
	6 women	26		LI Ex		1190	224	~−0.80			
Houmard et al., 1994 (23)[a]	13 men	30		Exercise	14	1505	154	−3.07[c]	NR	NR	NR
Kohrt et al., 1992 (26)	16 older men	25		Control	~45	—	—	0.08	NR	NR	NR
	47 older men	27		Exercise		1890	182	−0.78[b]			
	13 older women	24		Control		—	—	0.13			
	46 older women	25		Exercise		1120	182	−0.76[b]			
Schwartz et al., 1991 (42)[a]	13 young men	26		Exercise	27	2520	182	−0.67	−0.4 [0.7][c]	−0.8 [0.4][c]	−1.2 [0.4]
	15 older men	26		Exercise		1715	196	−1.19[c]	−1.3 [0.9][c]	−1.3 [0.7][c]	−2.6 [0.8]
Després et al., 1991 (8)[a]	13 women	34		Exercise	60	2450	406	NR	−0.1 [1]	−1.0 [0.2][c]	−1.1 [0.2]
Bouchard et al., 1994 (5)[a]	14 young men		24	Exercise	13	3500	357	NR	−2.2 [2.8][c]	−5.2 [2.1][c]	−7.4 [2.3]

Δ, change; VAT, visceral adipose tissue; ASAT, abdominal subcutaneous adipose tissue; TAAT, total abdominal adipose tissue (visceral + subcutaneous); HI Ex, high-intensity exercise; LI Ex, low-intensity exercise; NR, not reported.

[a] The exercise energy expenditure was not reported. The oxygen cost was estimated on the basis of the subjects $\dot{V}O_{2max}$, exercise intensity, frequency, and duration. Energy expenditure was subsequently determined by multiplying the oxygen cost by 5 $kcal \cdot L^{-1}$.

[b] Reduction in exercise group significantly greater than reduction in control group ($P < 0.05$).

[c] Significant within-group reduction ($P < 0.05$).

1 and 2 reveals that only three nonrandomized trials prescribed exercise for women of a magnitude greater than ~1500 $kcal \cdot wk^{-1}$. A rationale that would support the exclusion of women in studies wherein exercise is performed for longer durations is unknown. To the contrary, there is evidence to support the notion that women may be at an advantage when it comes to performing submaximal exercise. Indeed, during moderate-intensity long-duration exercise, females demonstrate a greater lipid and lower carbohydrate oxidation compared with men (7,45). A greater reliance on lipid as a fuel during submaximal exercise would spare muscle glycogen and thus, in theory, delay time to fatigue. Theses observations support the view that women are capable of performing moderate-intensity exercise of a sufficient duration and frequency to induce substantial weight loss.

As stated above, it is clear from Figure 1 that the weekly exercise-induced energy expenditure in the majority of studies reviewed in this analysis was low (e.g., <1500 $kcal \cdot wk^{-1}$). Indeed, for short-term studies the exercise programs prescribed resulted in an weekly energy expenditure that approximated 1850 kcal. Accordingly, the weekly weight loss averaged 0.2 kg for a total weight loss of 2.3 kg over 12 wk. This observation is consistent with the recent evidence-based review wherein it is concluded that physical activity alone in overweight and obese men and women reduces total (~2 kg) and abdominal fat (~2 cm) only modestly or not at all (31). From a clinical perspective, weight loss of this magnitude would be considered inconsequential by many and would do little to maintain motivation and adherence to a weight loss strategy that uses exercise alone. On the other hand, it is also clear from this review that overweight and obese persons (at least men) can sustain a weekly energy expenditure that is associated with a far more meaningful weight loss. Thus, if the goal is to use exercise alone as a strategy for obesity reduction, it is suggested that clinicians and practitioners prescribe exercise programs wherein the energy expended approximates a minimum of 3000–3500 $kcal \cdot wk^{-1}$. On the basis of data from our laboratory, this would require approximately 45–60 min of purposeful walking performed at a moderate intensity (~60% of peak $\dot{V}O_{2max}$ or 70% of maximum heart rate) on most days of the week (38). A program of this nature is not only consistent with recommendations related to the amount of physical activity required to improve cardiovascular health (32), but would result in substantial fat loss concurrent with the preservation of skeletal muscle and improvement in cardiovascular fitness (38).

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Chair summary and comments

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Speakers in this session addressed a number of biological and clinical entities that significantly contribute to the increasing burden of chronic degenerative diseases in developed and developing countries. By the design of the conference, these presentations were limited to reviewing the results of randomized controlled trials (RCTs). It became apparent during the session that RCTs addressing these outcomes provide limited data on relating dose of exercise to the magnitude of the outcome. However, many of these RCTs do report favorable changes in biological and clinical status resulting from endurance exercise training programs that typically involve exercise regimens recommended by the American College of Sports Medicine (1). Although the magnitude of the biological changes in many cases are relatively small (<15%), they still could confer a significant clinical benefit. This is especially true if a favorably clinical outcome from exercise is because of changes in more than one biological mechanism. This situation likely exists for exercise and coronary heart disease (CHD) mortality.

Kelley and Goodpaster report that patients who are sedentary with type 2 diabetes that participate in aerobic exercise training of moderate to hard intensity reduce hemoglobin (Hb) A1c concentrations by about 0.5–1.0% (a change required by the FDA for drugs approved for glucose control). This improvement is likely because of reduced insulin resistance of skeletal muscle. One large-scale RCT conducted in China reported a reduction in the rate of progression to diabetes from a status of impaired glucose tolerance. These data are consistent with various prospective observational studies reporting a lower incidence of type 2 diabetes in more active persons compared with the least active in the population. The results of some observational studies do support a dose-response relationship between amount of activity (especially the amount of more vigorous activity) and improvements in insulin sensitivity and glucose control. RCTs are needed to investigate the lower threshold of activity required to produce various biological and clinical outcomes.

The major finding reported (see Leon and Sanchez symposium article) in the session on lipids and lipoproteins was an increase in high-density lipoprotein (HDL)-cholesterol in response to aerobic training (average increase of 4.6%). This modest increase could have a significant effect on CHD, since a 1% increase in HDL-cholesterol is associated with a 3.5% decrease in mortality attributable to CHD (2). Few exercise RCTs have been conducted involving patients with hyperlipidemia, and the results for low-density lipoprotein (LDL)-cholesterol and triglyceride concentrations are mixed. Exercise-induced changes in HDL-cholesterol and triglyceride concentration are increased when accompanied by decreases in adiposity. It appears that training sessions lasting for longer periods (≥12 wk) have greater effect on lipoprotein concentrations than shorter programs, but other dose-response data were not presented.

Given the variety of outcome measures used in RCTs evaluating the effects of exercise on platelet aggregation and fibrinolysis, it is very difficult to obtain a consensus on how exercise affects these complex biological processes (see Raumara and colleague's symposium article). The few RCTs available report mixed results, but there are sufficient favorable data to warrant the support of well-designed RCTs of various exercise training regimens. Available data do not provide useful information on issues of dose-response. Discussion with no consensus occurred on the possible adverse effects of very-high-intensity exercise versus moderate-intensity exercise on hemostatic factors.

Reductions in body weight and body fat as a result of increased exercise appear to be proportional to the amount of aerobic exercise performed (see Ross and Janssen's symposium article). In RCTs lasting 16 wk or less where the exercise required an increase of ≥ 2200 kcal·wk^{-1}, an average weight loss of 2.5 kg was achieved. Smaller increases in exercise volume frequently obtained in studies of longer duration have resulted in inconsistent changes in body weight or fat. The distribution of fat loss (abdominal vs peripheral) is similar whether negative calorie balance is produced by caloric restriction or increased energy expenditure by exercise. Results of RCTs do not provide dose-response data for exercise intensity (independent of amount of exercise) and weight loss.

Well-designed RCTs are needed to further establish the efficacy of exercise for decreasing the clinical manifestations of type 2 diabetes, hyperlipidemia, and hemostatic abnormalities. For all outcomes considered in this session, RCTs are needed to establish the exercise dose-response relationship, especially for exercise intensity and amount. Data are needed to establish the lower threshold for exercise intensity and amount for each of these outcomes.

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Physical activity and cancer risk: dose-response and cancer, all sites and site-specific

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ABSTRACT

THUNE, I., and A. S. FURBERG. Physical activity and cancer risk: dose-response and cancer, all sites and site-specific. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S530–S550. **Purpose:** The association between physical activity and overall and site-specific cancer risk is elaborated in relation to whether any observed dose-response association between physical activity and cancer can be interpreted in terms of how much physical activity (type, intensity, duration, frequency) is needed to influence site- and gender-specific cancer risk. **Methods:** Observational studies were reviewed that have examined the independent effect of the volume of occupational physical activity (OPA) and/or leisure time physical activity (LPA) on overall and site-specific cancer risk. **Results:** The evidence of cohort and case-control studies suggests that both leisure time and occupational physical activity protect against overall cancer risk, with a graded dose-response association suggested in both sexes. Confounding effects such as diet, body weight, and parity are often included as a covariate in the analyses, with little influence on the observed associations. A crude graded inverse dose-response association was observed between physical activity and colon cancer in 48 studies including 40,674 colon/colorectal cancer cases for both sexes. A dose-response effect of physical activity on colon cancer risk was especially observed, when participation in activities of at least moderate activity (>4.5 MET) and demonstrated by activities expressed as MET-hours per week. An observed inverse association with a dose-response relationship between physical activity and breast cancer was also identified in the majority of the 41 studies including 108,031 breast cancer cases. The dose-response relationship was in particular observed in case-control studies and supported by observations in cohort studies when participation in activities of at least moderate activity (>4.5 MET) and demonstrated by activities expressed by MET-hours per week. This association between physical activity and breast cancer risk is possibly dependent on age at exposure, age at diagnosis, menopausal status and other effect modifiers, e.g., body mass index. Furthermore, data concerning carcinoma of other cancers (prostate, lung, endometrium, ovary, and testicular cancers) are required. **Conclusion:** A protective effect of physical activity on site-specific cancer risk with a dose-response association between physical activity and colon and pre- and postmenopausal breast cancer supported by identified biological mechanisms has been observed. The optimal permutation of type, intensity, duration, and frequency of physical activity across the lifespan is unclear, but it is gender, age, and site specific and supports moderate activity (>4.5 MET) more than light activities (<4.5 MET). The complicated nature of the physical activity variable, combined with lack of knowledge regarding possible biological mechanisms operating between physical activity and cancer, warrants further studies including controlled clinical randomized trials. **Key Words:** PHYSICAL ACTIVITY, CANCER RISK, BIOLOGICAL MECHANISMS, DOSE-RESPONSE

Environmental exposure has been accepted as a major causal factor of cancer (80–90%) (67). Our genetic constitution was selected for a lifestyle characterized by physical activity. People who have a sedentary Western lifestyle in the year 2000 may be about 0.003% different genetically from late Stone Age people of 10,000 yr ago (104). Consequently, a sedentary lifestyle may be one explanation for the variation in cancer incidence rates and changes in incidence rates observed in migration studies between and within countries and among subgroups of people.

Although Rammazzini 300 yr ago suggested that physical activity played a role in human cancer etiology (95), it is mainly in the last decade that investigators, encouraged by the findings of animal studies, have linked physical activity to human cancer risk (101). This evidence comes from observational studies, as no intervention studies so far have been

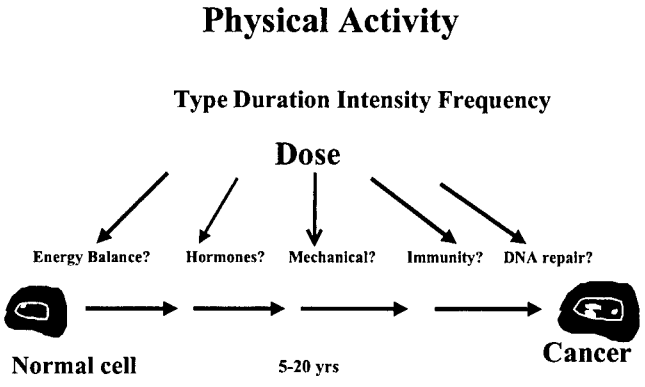


FIGURE 1—Hypothesis of the influence of dose of physical activity (type, duration, intensity, frequency) on possible biological mechanisms operating on cancer development.

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TABLE 1. Studies on physical activity and overall cancer risk, dose-response.

Cohort Study	Study Population	Total (*M*)	Follow-Up Time	Age at Baseline (yr)	Cases (*M*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Albanes et al., 1989 USA (1)	National Health and Nutrition Survey	M 5141 F 7407	7–13	25–74	M 460 F 399 (Incidence)	Questionnaire (LPA, OPA)			0.5 (0.4–0.8) 0.8 (0.6–1.3)		S NS		C
Arraiz et al., 1992 Canada (4)	Canada fitness survey	M + F 42,239	7	30–69	165 (Fatal)	Questionnaire (LPA, OPA) Fitness	0.8 (0.5–1.4) LPA 0.5 (0.2–1.3) Fitness			NS			C
Blair et al., 1989 USA (8)	Texas Cooper clinic	M + F 13,344	8	20+	82 (Fatal)	Fitness—treadmill	M: 0.2 S F: 0.2 S			S S			C
Chang-Claude et al., 1993 Germany (16)	Vegetarian	M + F 1904	11	?	304 (Fatal)	Questionnaire (LPA)	1.0 (0.3–3.0)			NS			C
Clemmesen, 1998 Denmark (19)	Copenhagen, male	M 5248	15	40–59	980 (Incidence)	Questionnaire (LPA) Fitness	0.9 (0.8–1.1) 0.8 (0.6–1.0)			NS $P = 0.08$			C
Garfinkel and Stellman, 1988 USA (32)	Cancer prevention study, 50 states	M + F 868,620	2	30+	1355 992 (Fatal)	Questionnaire (LPA)	M: SMR = 99 F: SMR = 120			— —			C
Kampert et al., 1996 USA (50)	Texas Cooper clinic	M 25,341 F 7080	8	20–82	179 44 (Fatal)	Questionnaire (LPA) Fitness	0.2 (0.1–1.1) 0.4 (0.2–0.6) 2.9 (0.6–13.2) 0.5 (0.2–1.8)			S S NS $P = 0.07$			C
Keys et al., 1985 Seven countries (52)	Europe, USA, Asia	M 11,325	15	40–59	594 (Fatal)	Interview (LPA)	NS			—			C
Leon and Connett, 1991 USA (63)	MRFIT (Multiple Risk Factor Intervention Trial)	M 12,138	10.5	35–57	265 (Fatal)	Questionnaire (LPA)	0.8 (0.7–1.3)			NS			C
Menotti and Seccareccia, 1985 Italy (79)	Railroad workers, Italy	M 99,029	5	40–59	795 (Fatal)	Occupation (OPA) Energy expenditure (kcal)		NS		—			C
Paffenbarger et al., 1987 USA (89)	A) San Francisco longshoremen B) Harvard alumni	M 3686 M 16,936	12–22 12–16	35–74	270 (Fatal) 446	Occupational title (OPA) Physical activity (kcal)	0.9 NS Significant decreased risk			S			C
Persky et al., 1981 USA (92)	Gas company, Chicago (3 groups: A, B, C)	M 8916	25	40–64	8916 (Fatal)	Resting heart rate ≤70 vs >80 (OPA)	Significant protective			S			C
Polednak, 1976 USA (93)	Retrospective cohort Death certificate	M 8393			1076 (Fatal)	College athletics	Suggestive increased risk			NS			C
Smith et al., 2000 UK (107)	Whitehall study	M 6702	25	40–64	832 (Fatal)	Questionnaire Self-report (LPA) Walking pace	0.8 (0.6–0.9)			S			C
Steenland et al., 1995 USA (108)	National Health and Nutrition Survey	M + F 14,407		25–74	657 593 (Incidence)	Heart rate 73< vs 80+ (OPA)	M: 0.8 (0.6–1.0) F: 1.0 (0.8–1.3)	No effect (OPA) No effect (OPA)			S NS		C
Taylor et al., 1962 UK (115)	Railroad workers	M 191,609	25	40–64	? (Fatal)	Job classification (OPA) Section men vs clerks	0.7 (0.6–0.7)			S			C
Wannamethee et al., 1993 UK (127)	British patients	M 7735	9.5	40–64	225 (Fatal)	Questionnaire Self-report (LPA) Heart rate: 60 vs 90	0.6 (0.4–0.9) LPA 0.4 (0.3–0.7) Heart rate			S S			C

RR, relative risk; CI, confidence interval; LPA, leisure time physical activity; OPA, occupational physical activity; S, significant ($P > 0.05$); NS, nonsignificant; M, males; F, females; SMR, Standardized Mortality Ratio.

TABLE 2. Studies on physical activity and colorectal, colon, and rectal cancer risk, dose-response.

Cohort Studies	Study Population	Total (*M*)	Follow-Up Time	Age at Baseline (yr)	Cases (*M*)	Physical Activity Assessment—Dose	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Albanes et al., 1989 USA (1)	National Health and Nutrition Survey	M 5138 F 7407	7–13	25–74	62 CR 66 CR	Questionnaire Interview (LPA, OPA)	1.0 (0.5–2.0) CR 0.8 (0.4–1.7) CR	0.6 (0.3–1.4) CR 1.4 (0.5–3.3) CR		NS NS	NS NS		C
Ballard-Barbash et al., 1990 USA (5)	Framingham	M 1906 F 2308	28	30–62	73 CR 79 CR	Questionnaire Physician Interview (LPA)	0.6 (0.3–1.0) CR 0.9 (0.6–1.7) CR			— —			C
Bostick et al., 1994 USA (9)	Iowa	F 3215	5	55–69	212 C	Questionnaire Self-report (LPA)	1.1 (0.7–1.5) C			NS			C
Chow et al., 1993 China (18)	Shanghai 1980–84	M + F 83,202	1980–84	All	M 2291 C F 936 C	Occupational Category (OPA)		M: 0.8 (0.7–0.9) C F: 0.9 (0.8–1.0) C			S S		C
Clemmesen, 1998 Denmark (19)	Copenhagen male Cohort	M 5248	15	40–59	88 C 55 R	Questionnaire (LPA)			0.5 (0.3–0.8) C 0.9 (0.4–2.0) R	S NS			C
Gerhardsson et al., 1986 Sweden (36)	Population	M 1.1 million	19	20–64	5100 C 4533 R	Questionnaire Self-report Occupation (OPA, LPA)		0.8 (0.7–0.9) C (Prox) 0.9 (0.8–1.0) R			— —		C
Gerhardsson et al., 1988 Sweden (37)	Swedish twin registry	M + F 164,777	14	42–81	M 99 C F 92 C	Questionnaire Self-report (OPA, LPA)			M + F: 0.3 (0.1–0.8)			—	C
Giovannucci et al., 1995 USA (39)	Health professionals	M 47,273	6	40–75	203 C	Questionnaire Self-report (LPA)	0.5 (0.3–0.9) C			S			C
Hsing et al., 1998 USA (46)	Lutheran Brotherhood Insurance society	M 17,633	20	Not stated	120 C 25 R	Occupational title (OPA)		0.4 (0.2–0.9) C			—		C
Lee et al., 1991 USA (58)	Harvard alumni	M 17,148	23	30–79	225 C 44 R	Questionnaire Self-report (LPA)	0.5 (0.3–0.9) C 1.7 (0.4–7.7) R				NS NS		
Lee et al., 1994 USA (60)	Harvard alumni	M 17,607	26	30–79	280 C 53 R	Questionnaire Self-report (LPA)	0.9 (0.5–1.6) C 2.8 (0.5–15.1) R			NS NS			C
Lee et al., 1997 USA (61)	Physicians	M 21,807	10.9	40–84	217 C	Questionnaire Self-report (LPA)	1.1 (0.7–1.6) C			NS			C
Lynge and Thygesen, 1988 Denmark (71)	Population census	M + F 2 million	11	20–64	Not stated	Occupational title (OPA)		M: 0.7 (0.5–0.9) C 1.0 (0.7–1.7) R F: 0.6 (0.4–0.9) C 1.6 (0.6–5.0) R			— — — —		C
Marti and Minder, 1988 Switzerland (75)	Population		4		1995 C 1066 R	Occupational title (OPA)		0.7 S					C
Martinez et al., 1997 USA (76)	Nurses Health Study	F 52,875	16	30–55	608 C	Questionnaire Interview (LPA)	Tot: 0.5 (0.3–0.9) Dist: 0.3 (0.1–0.8) Prox: 0.8 (0.4–1.6)			S S			C
Paffenbarger et al., 1987 USA (89)	A) College students B) Longshoremen	M 51,977 F 4706 M 6351		35–70	M + F 201 C 53 R 21 CR	Questionnaire (LPA) Occupational (OPA)	0.9 C 0.5 R $P < 0.05$	1.2 CR		— —	NS		C C
Severson et al., 1989 USA (100)	Japanese men on Hawaii	M 8006	18–21	46–68	192 C 194 R	Questionnaire Self-report (OPA, LPA)	0.7 (0.5–0.9) C 0.7 (0.5–1.1) R	0.7 (0.5–1.0) C 1.2 (0.7–2.2) R	0.7 (0.5–1.0) C 1.4 (0.8–2.4) R	NS NS	NS NS	NS NS	C
Steenland et al., 1995 USA (108)	National Health and Nutrition	M + F 14,407	13–17	25–74	M 94 CR F 82 CR	Questionnaire Self-report		1.1 (0.7–1.7) CR 0.7 (0.4–1.3) CR			— —		C
Suicidani et al., 1993 Denmark (110)	Population	M 5249	18	40–59	51 C 42 R	Questionnaire Self-report (OPA, LPA)	No effect C No effect R			— —	— —		C
Thune and Lund, 1996 Norway (119)	Population	M 53,242 F 28,274	16.3 15.5	40–54 40–54	236 C 170 R 99 C 58 R	Questionnaire Self-report (OPA, LPA)			M: 1.0 (0.6–1.5) C >45 yr: 0.7 (0.4–1.1) C No effect rectal F: 0.6 (0.4–1.0) C No effect rectal			NS S S NS	C
Vena et al., 1985 USA (123)	Retrospective cohort				M 6459 C F 604 C	Occupational title (OPA)		0.9 $P < 0.05$ 0.8 $P < 0.05$			—		C

TABLE 2. *Continued*

Case-Control Studies	Study Population	Sources of Controls	Age (yr)	Controls	Cases *N*	Physical Activity Assessment—Dose	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Will et al., 1998 USA (132)	Population Cancer prevention, 25 states	M 342,859 F 510,850	13	30+	3218 CR 4006 CR	Questionnaire Self-report (LPA, OPA)			M: 0.7 (0.6–0.9) CR F: 0.9 (0.8–1.1) CR		—		C
Wu et al., 1987 USA (133)	Retirement cohort	M + F 11,888	4.5		M 58 CR F 68 CR	Questionnaire Self-administered (LPA)	M: 0.4 (0.2–0.8) CR F: 0.9 (0.5–1.6) CR			S NS			C
Arbman et al., 1993 Sweden (3)	Hospital	Hospital and population registries	<75	M + F 371 Hosp 430 Pop	M 51 C 48 R F 47 C 31 R	Occupational (OPA)		1.1 (0.6–2.0) C 2.1 (1.2–3.9) R			— —		C
Benito et al., 1990 Spain (6)	Majorca	Population	<80	M 295 F 203	M 72 C 73 R F 72 C 56 R	Questionnaire Self-report (OPA)		M + F: 0.7 S			S		C
Brownson et al., 1989 USA (10)	Missouri Cancer Registry	Other cancer registry patients	20+	M 9965	1993 C	Occupation (OPA)		0.7 (0.5–1.0) C			S		C
Brownson et al., 1991 USA (11)	Missouri Cancer Registry	Other cancer registry patients	All		1838 C 812 R	Occupation (OPA)		0.8 (0.7–1.0) C 0.8 (0.6–1.3) R			S NS		C
Dosemeci et al., 1993 Turkey (25)	Turkey hospitals	Hospital based	All	M 486	93 C 120 R	Occupational title (OPA)		0.6 (0.7–1.0) C 0.7 (0.3–1.4) R			S NS		C
Fraser and Pearce, 1993 New Zealand (27)	New Zealand Cancer Registry	Population based			M 1651 C 1046 R	Occupation code (OPA)		0.8 (0.7–1.0) C 0.8 (0.7–1.0) R			— —		C
Fredriksson et al., 1989 Sweden (29)	Swedish Cancer Registry	Population	30–75	M 306 F 317	156 C 156 C	Occupational history (OPA)		0.8 $P < 0.05$ C 0.7 $P < 0.05$ C			— —		C
Garabrant et al., 1984 USA (35)	Incidence	Population based	20–64	M	2950 C 1213 R	Occupation code (OPA)		0.6 (0.6–0.8) C 1.1 (0.9–1.6) R			— —		C
Gerhardsson et al., 1990 Sweden (38)	Population hospitals + registry	Population	40–79	M + F 624	M 163 C M 107 R F 189 C F 110 R	Questionnaire Self-report (OPA, LPA)			0.6 (0.2–1.7) C 1.1 (0.4–3.3) R 0.4 (0.2–1.1) C 0.7 (0.2–2.0) R			— — — —	C
Kato et al., 1990 Japan (51)	Hospitals	Hospital		M + F 528	132 C 91 R	Questionnaire (LPA) Self-report (OPA)	0.6 (0.3–0.9) C 0.5 (0.3–1.0) R	0.5 (0.3–0.9) C 0.7 (0.4–1.4) R					C
Kune et al., 1990 Australia (55)	Melbourne	Population		M 398 F 329	388 CR 328 CR	Questionnaire Interview (LPA, OPA)			1.5 (0.8–2.7) CR 0.9 (0.3–2.8) R 1.6 (0.8–3.2) CR 1.9 (0.5–6.6) R			— — — —	C
Le Marchand et al., 1997 USA (57)	Hawaii 1987–91	Population based	All	M 698 CR F 494 CR	698 CR 494 CR	Questionnaire Interview (LPA, OPA, lifetime)			0.7 (prox) 0.5 0.6 (prox) 0.8	NS NS S NS			C
Levi et al., 1999 Switzerland (66)	Hospitals 1992–97	Hospital based	35–74	M 211 F 280	65 C 74 R 67 C 37 R	Questionnaire Interview (LPA, OPA)	30–39 years M + F 0.4 (0.3–0.7) CR	0.5 (0.3–0.9) CR		S	S		C
Longnecker et al., 1995 USA (69)	Hospital + registry	Population	≥31	M 703	163 C 242 R	Questionnaire Interview (LPA, OPA)	0.6 (0.4–1.0) C 1.2 (0.7–2.0) R	0.7 (0.3–1.5) C 1.0 (0.4–2.2) R		NS NS	NS NS		C
Marcus et al., 1994 USA (72)	Wisconsin Cancer Registry	Driver's license Medicare	<75	F 2135	536 C	Questionnaire Interview (LPA, OPA)			Early adulthood 0.5 (0.2–1.1) C			N	C
Marckowitz et al., 1992 USA (74)	Hospital New York	Hospitals	All	M 1164	308 C 135 R	Questionnaire Interview (OPA)		0.5 (0.3–0.8) C 0.6 (0.3–1.1) R			S S		

TABLE 2. *Continued*

Case-Control Studies	Study Population	Sources of Controls	Age (yr)	Controls	Cases *N*	Physical Activity Assessment—Dose	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Peters et al., 1989	Cancer Registry	Neighborhood	<45	M 147	147 C	Questionnaire		0.9 (0.4–2.0) CR			—		C
USA (91)	Los Angeles			F 41	41 R	Interview (OPA)		1.4 (0.4–5.0) R			—		
Slattery et al., 1988	Utah Cancer	Population	40–79	M 180	110 C	Questionnaire	0.3 (0.1–0.7) C		0.7 (0.4–1.3) C		—		C
USA (105)	Registry	based		F 204	119 C	Self-report (OPA, LPA)	0.5 (0.3–0.9) C		0.5 (0.3–0.9) C		—		
Slattery et al., 1997	Different States in	Population		M 1099	1290 C	Questionnaire	0.6 (0.5–0.8) C			S			C
USA (106)	USA	based		F 894	1120 C	Interview (LPA)	0.6 (0.5–0.8) C			S			
Tang et al., 1999	Taiwan Medical	Hospital	33–80	M 92	92 CR	Questionnaire	0.3 (0.1–0.8) CR			S			C
Taiwan (113)	Centre	based		F 71	71 CR	Interview (LPA)	0.2 (0.–0.8) C			S			
							0.4 (0.1–1.5) R			NS			
							0.8 (0.3–1.9) CR			NS			
							0.6 (0.2–2.2) C			NS			
							0.8 (0.3–2.5) R						
Tavani et al., 1999	6 Italian areas	Hospital	19–74	M 2073	688 CR	Questionnaire		0.6 (0.4–0.9) C			S		C
Italy (114)		based		F 2081	435 R	Interview (LPA, OPA)		1.3 (0.8–2.0) R			NS		
					537 CR			0.5 (0.3–0.7) C			S		
					286 R			0.9 (0.5–1.6) R			NS		
Thun et al., 1992	Nested case-control	Population		M 3051	611 C	Questionnaire			0.6 (0.3–1.3) C			S	C
USA (117)		based		F 2695	539 C	Self-report (LPA, OPA)			0.9 (0.4–2.0) C			NS	
Vena et al., 1987	Hospital patients	Noncancer	30–79	M 1431	210 C	Occupational (OPA)		0.5 $P < 0.05$		S			C
USA (124)		patients			276 R			1.2 NS		S			
White et al., 1996	Cancer Registry	Population	30–62	M 233	251 C	Questionnaire	0.6 (0.4–0.9) C	No effect		S			C
USA (129)	Seattle			F 194	193 C	Interview (LPA, OPA)	0.7 (0.4–1.3) C	No effect		NS			
Whittemore et al., 1990	Canada, China	Population	20+	M 1376	274 C	Questionnaire	USA: 0.6 (0.4–0.9) C	USA: 0.4 (0.2–0.9) C		S	S		C
Canada (130)		based		F 1112	236 R	Interview (LPA, OPA)	0.7 (0.4–1.1) R	0.6 (0.2–1.8) R		S	S		
					192 C		China: 1.2 (2.6–0.5) C	China: 0.7 (0.3–1.7) C		S			
					203 R		1.4 (0.6–3.1) R	1.2 (0.6–2.5) R					
							USA: 0.5 (0.3–0.8) C	USA: 0.8 (0.3–2.3) C					
							0.5 (0.3–1.0) R	1.2 (0.5–3.1) R					
							China: 0.4 (0.2–1.0) C	China: 0.6 (0.2–1.7) C					
							1.5 (2.9–0.7) R	1.7 (0.6–5.0) R					

RR, relative risk; CI, confidence interval; LPA, leisure time physical activity; OPA, occupational physical activity; S, significant ($P > 0.05$); NS, nonsignificant; M, males; F, females; C, colon cancer (except in Evidence Category column); R, rectal cancer.

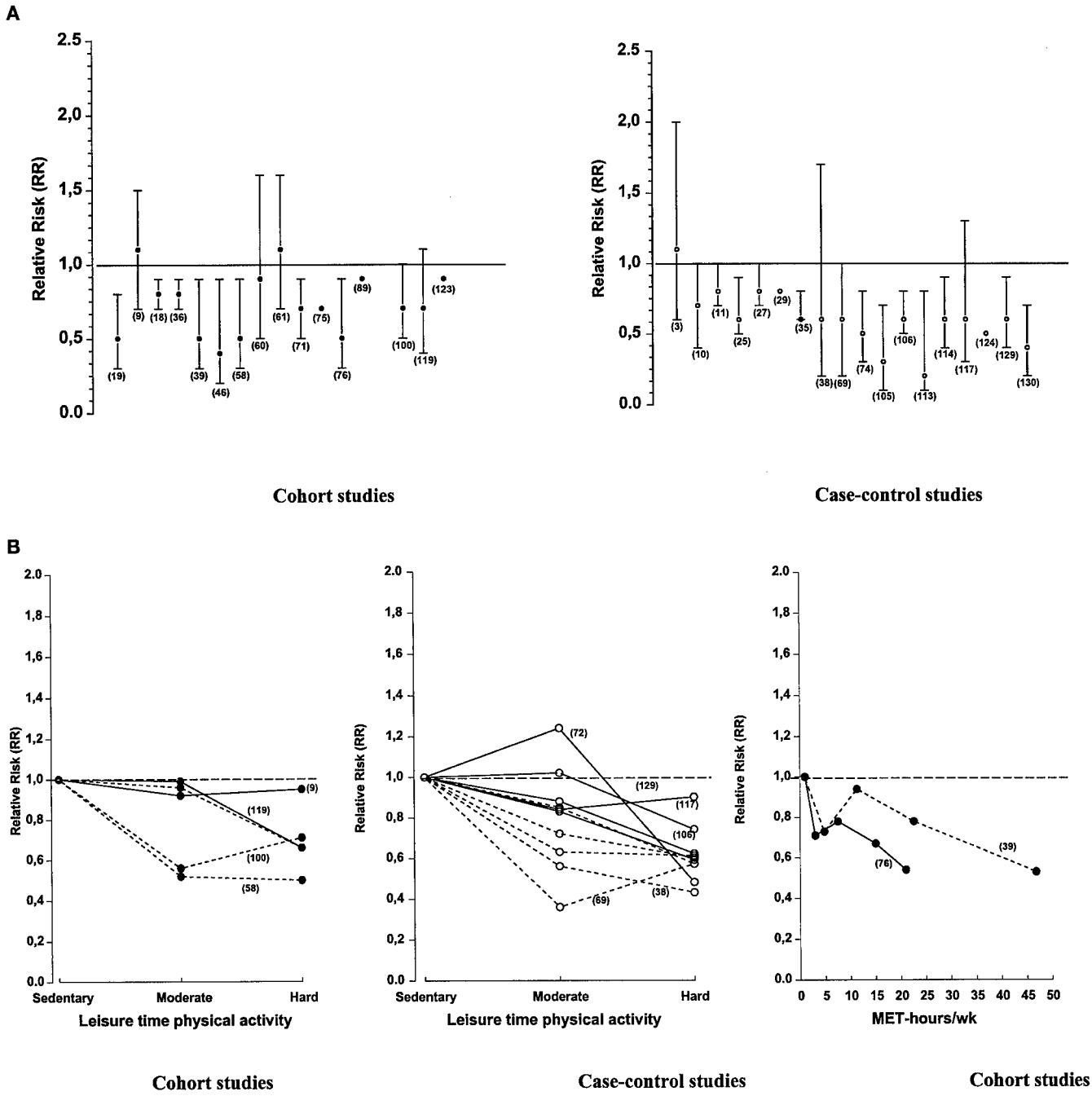


FIGURE 2—(A) Relative risk of colon cancer with 95% confidence intervals among persons with high versus low physical activity (LPA and OPA) in cohort (●) and case-control studies (○) (see references). (B) The dose-response relationship between LPA (categories and MET-hours per week) and colon cancer risk in cohort and case-control studies (see references) including > 100 colon cancer cases. Males (dashed lines): cohort studies (●) and case-control studies (○). Females (solid lines): cohort studies (●) and case-control studies (○).

conducted on physical activity for the primary prevention of cancer. Although many studies suggest an association between physical activity and cancer risk (overall and site-specific), the precise quantitative characteristics of a potential threshold effect or the dose-response remains undefined. Therefore, the aim of the present study was to examine whether there is a dose-response between total volume of physical activity and indexes of morbidity and mortality of overall and site-specific cancer risk and, furthermore, to elucidate quantitative characteristics of the identified dose-response relations of importance in primary prevention. Even a small protective effect of physical activity on cancer risk may be of considerable importance for public health as the population ages and a sedentary lifestyle increases worldwide.

METHODS

Studies were identified through a systematic review of published literature available on the MEDLINE and PubMed literature databases and also by hand searching relevant journals through August 2000. The general

TABLE 3. Studies on physical activity and breast cancer risk, dose-response.

Cohort Studies	Population	Total (*N*)	Follow-Up Time	Age at Baseline (yr)	Cases (*N*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Albanes et al., 1989 USA (1)	National Health and Nutrition Survey	7407	7–13	25–74	122	Questionnaire Interview (LPA, OPA)	1.0 (0.6–1.6)	0.9 (0.5–1.7)		NS	NS		C
Calle et al., 1998 USA (12)	Population Iowa	563,395	9	≥29	1780 (Fatal)	Questionnaire Self-report (OPA)		1.1 (1.0–1.3)			—		C
Cerhan et al., 1998 USA (15)	Population Iowa 65+	1806	20	65–102	46	Questionnaire Interview (LPA, OPA)	0.2 (0.2–0.9)					—	C
Dorgan et al., 1994 USA (24)	Population	2307	28	≥35	117	Questionnaire Interview (LPA, OPA)			1.6 (0.9–3.0)			NS	C
Fraser and Shavlik, 1997 USA (28)	Adventists	20,341	6	≥24	218	Questionnaire Self-report (LPA, OPA, lifetime)			0.7 (0.5–0.9)			—	C
Frisch et al., 1987 USA (31)	College alumni	5398	1–56	18–22	69	Questionnaire Self-report College athletics	0.5 (0.3–1.0)			—			C
Moore et al., 2000 USA (83)	Population sample Iowa driver's license	37,105	12	55–69	1380	Questionnaire Self-report (LPA)	0.9 (0.8–1.1)			—			C
Moradi et al., 1999 Sweden (85)	Population census	1,940,510	18	All ages	51,520	Occupational titles (OPA)		50–59 yr 0.8 (0.6–0.9)			S		C
Paffenbarger et al., 1987 USA (89)	College alumni	4706	28–52	18–22	46	Questionnaire Self-report College athletics (LPA)	0.96 ($P = 0.92$)			NS			C
Pukkala et al., 1993 Finland (94)	Teachers' college alumni	10,038	24	18–22	228	Self-report College athletics	0.7 (0.6–0.8)			—			C
Rockhill et al., 1998 USA (97)	Nurses	116,671	16	25–42	372	Questionnaire Self-report (LPA)	Adolescent: 1.1 (0.8–1.6) Recent: 1.1 (0.8–1.5)			NS			C
Rockhill et al., 1999 USA (98)	Nurses	121,701	31	30–35	3137	Questionnaire Self-report (LPA)	0.8 (0.7–0.9)			S			C
Sesso et al., 1998 USA (99)	College alumni	1566	31	≥40	109	Questionnaire Self-report (LPA)	Tot: 0.7 (0.5–1.4) Pre: 1.8 (0.8–4.3) Post: 0.5 (0.3–0.9)			NS NS S			C
Steenland et al., 1995 USA (108)	National Health and Nutrition Survey	14,407	13–17	25–74	163	Questionnaire Interview (LPA, OPA)			0.9 (0.5–1.6)				C
Thune et al., 1997 Norway (120)	Population sample	25,624	13.7	20–54	351	Questionnaire Self-report (LPA, OPA)	Tot: 0.6 (0.4–1.0) Pre: 0.5 (0.3–1.1) Post: 0.7 (0.4–1.1)	0.5 (0.3–0.9) 0.5 (0.2–1.0) 0.8 (0.5–1.2)		S NS NS	S S NS		C
Vena et al., 1987 USA (124)	Population sample Washington	25,000	5	All	791 (Fatal)	Occupational titles (OPA)	0.85 ($P < 0.05$)				—		C
Wyshak and Frisch, 2000 USA (134)	College alumni	5398	15	21–80	175	Questionnaire Self-report College athletics	Tot: 0.6 (0.4–0.8) <45 yr: 0.2 (0.0–0.6)			—			C
Zheng et al., 1993 China (136)	Population sample Census 1980–84		5	27–36	2736	Occupational titles (OPA)		SIR = 0.79 $P < 0.05$			—		C

Case-Control Studies	Study Population	Sources of Controls	Age	Controls (*N*)	Cases (*N*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Bernstein et al., 1994 USA (7)	Los Angeles population	Neighborhood	≤40	545	545	Questionnaire Interview (LPA, lifetime)	0.4(0.3–0.6)			S			C
Carpenter et al., 1999 USA (13)	Los Angeles population	Neighborhood	55–64	904	1123	Questionnaire Interview (LPA, lifetime)	0.4(0.2–0.8)			S			C
Chen et al., 1997 USA (17)	Seattle population	Population based	21–45	961	747	Questionnaire Interview (LPA, lifetime)	0.9(0.3–2.6)			NS			C

TABLE 3. *Continued*

Case-Control Studies	Study Population	Sources of Controls	Age	Controls (*N*)	Cases (*N*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Coogan et al., 1996 USA (20)	Cancer registries Population	Driver's license, Medicare	<75	9453	6835	Occupational titles (OPA)		1.2 (1.1–1.2)			—		C
Coogan et al., 1997 USA (21)	4 state cancer registries	Driver's license, Medicare	<74	6783	4863	Telephone interview (OPA)		0.8 (0.6–1.1)			S		C
Coogan et al., 1999 USA (22)	General population	Population based	All	670	233	Telephone Interview (OPA)		Heavy jobs: <10 yr 0.7 (0.4–1.3) ≥ 10 yr 1.7 (0.9–3.3)			NS		C
D'Avanzo et al., 1997 Italy (23)	General population	Hospital based	23–74	2588	2569	Questionnaire Interview (LPA, OPA)	0.7 (0.4–1.1)	0.6 (0.4–1.0)		NS	S		C
Dosemeci et al., 1993 Turkey (25)	Hospitals	Hospital based	All	244	241	Occupation (OPA)		1.4 (0.3–3.5)			NS		C
Friedenreich et al., 1995 Australia (30)	Population	Population voters	20–74	Pre: 110 Post: 258	Pre: 110 Post: 258	Questionnaire Interview (LPA)	Tot: 0.7 (0.5–1.1) Pre: 0.6 (0.3–1.1) Post: 0.7 (0.4–1.2)			NS NS NS			C
Gammon et al., 1998 USA (34)	Cancer registries	Population based	<45	3173	1668	Questionnaire (LPA)	1.0 (0.8–1.3)			NS			C
Hirose et al., 1995 Japan (43)	Hospitals	Hospital based	All	Pre: 14,864	Pre: 606	Questionnaire	Pre: 0.7 (0.6–1.0)			—			C
Hu et al. 1997 Japan (47)	Population	Screened population	All	Pre: 202 Post: 2060	Pre: 87 Post: 3557	Questionnaire Self adm Activity (LPA) teens/20's	Pre: 0.7 (0.4–1.4) 1.0 (0.5–1.9) Post: 1.4 (0.6–3.1) 0.5 (0.2–1.5)			NS NS NS NS			C
Kocic et al., 1996 Serbia (53)	Population	Hospital based	All	116	116	Questionnaire Self adm (LPA)	T=2.72 $P < 0.008$			—			C
Levi et al., 1999 Switzerland (65)	Lausanne population	Hospital based	<75	374	246	Questionnaire Interview (LPA, OPA)	15–19 yrs: 0.4 (0.3–0.7) 30–39 yrs: (0.3–0.8) 50–59 yrs: 0.4 (0.2–0.8)	15–19 yrs: 0.6 (0.4–1.0) 30–39 yrs: 0.5 (0.3–1.0) 50–59 yrs: 0.7 (0.4–1.3)		S	S		C
Marcus et al., 1999 USA (73)	North Carolina population	Motor vehicle list/ Medicare list	20–74	864	790	Questionnaire Interview (LPA, household)	At age 12: 0.8 (0.6–1.1)			NS			C
McTirnan et al., 1996 USA (77)	Washington population	Random digit dialing population	50–64	492	537	Questionnaire Interview (LPA)	0.6 (0.4–1.0)			S			C
Mezzetti et al., 1998 Italia (80)	Italy 6 areas	Hospital based	23–74	2588	2569	Questionnaire Interview (OPA)		Pre: 0.7 (0.5–1.1) Post: 0.6 (0.5–0.9)			S		C
Mittendorf et al., 1995 USA (82)	4 Different states population	Motor vehicle, Medicare list	18–74	9539	6888	Questionnaire Self adm (LPA, OPA)	0.5 (0.4–0.7)			S	S		C
Moradi et al., 2000 Sweden (86)	Population	Population based	50–74	3455	3347	Questionnaire Self report (LPA, OPA) Recent/45–54 age	0.8 (0.7–0.9) 0.7 (0.5–1.0)			S			C
Shoff et al., 2000 USA (102)	4 States population	Population based	All	5817	4614	Questionnaire Interview (LPA) 14–22 age	0.2 (0.1–0.7)			S			C
Taioli et al., 1995 USA (112)	New York hospitals	Hospital based	All	531	617	Questionnaire Interview (LPA)	1.0 (0.6–1.8)			—			C
Ueji et al., 1998 Japan (122)	Resident rolls	Hospital based	All	236	148	Questionnaire Interview (LPA, OPA)	Tot: 0.4 (0.2–0.7) Pre: 0.3 (0.1–1.0) Post: 0.5 (0.1–1.6)	Tot: 0.6 (0.3–1.1) Pre: 0.6 (0.2–2.3) Post: 0.7 (0.2–1.9)		S NS NS	NA NS NS		C
Verloop et al., 2000 Netherlands (126)	Population	Population based	20–54	918	918	Questionnaire Interview (LPA, OPA)	0.7 (0.6–0.9)			S			C

RR, relative risk; CI, confidence interval; LPA, leisure time physical activity; OPA, occupational physical activity; S, significant ($P > 0.05$); NS, nonsignificant.

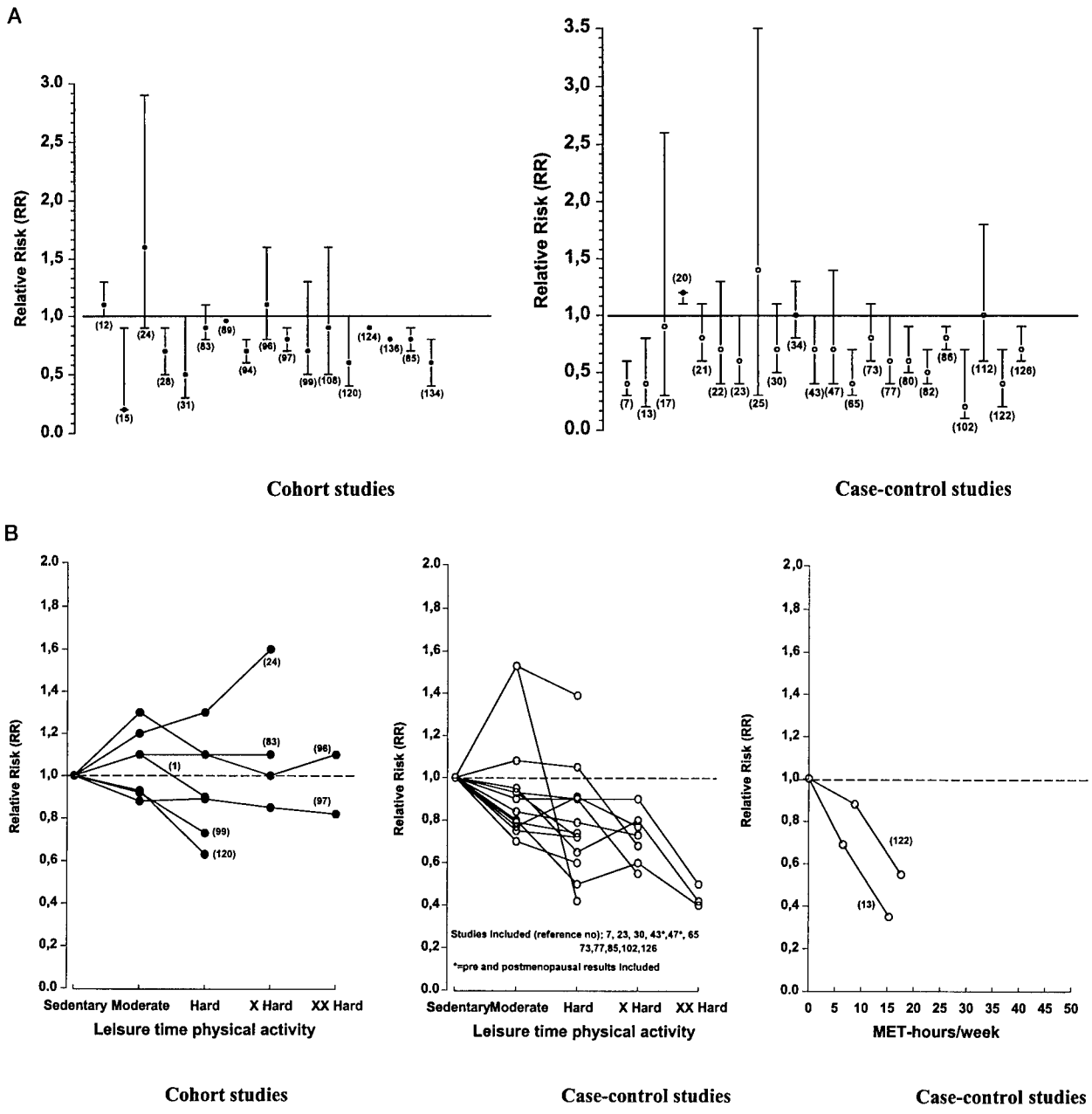


FIGURE 3—(A) Relative risk of breast cancer with 95% confidence intervals among persons with high versus low physical activity (LPA and OPA) in cohort (●) and case-control studies (○) (see references). (B) The dose-response relationship between LPA (categories and MET-hours per week) and breast cancer risk in cohort and case-control studies (see references) including > 100 breast cancer cases. Females—cohort studies (●) and case control studies (○).

inclusion criteria were 1) studies focusing on primary prevention of overall and/or site-specific cancer; 2) a quantitative description of the physical activity variable was described; and 3) the outcome measures including indexes of morbidity and mortality for overall and/or site-specific cancer.

A dose-response relationship was especially elaborated in relation to colon and breast cancer in studies including > 100 cases, respectively. Multiple results from the same study were included only if they contained other characteristics of the exposure variable (physical activity) or the relevant cancer type. Comparisons are made between studies using a great variety of, sometimes crude, physical assessments and a great variety in the characteristics of the populations studied.

Physical Activity and Overall Cancer Risk

Physical activity has marked effects on many functions of the human body, which may influence overall cancer risk (54). These effects include direct mechanical processes such as improved circulation, ventilation and bowel transit time, improved energy balance and immune function, and possibly the capacity to perform DNA repair (Fig. 1).

Among the 17 observational studies identified (Table 1), all were follow-up studies, most contained information on

TABLE 4. Studies on physical activity and endometrial cancer risk, dose-response.

Cohort Studies	Study Population	Total (*N*)	Follow-Up Time	Age at Baseline (yr)	Cases (*N*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Moradi et al., 1998 Sweden (84)	Record linkage	1,440,839	19	16–95	12,332	Occupational title (OPA)		0.8 (0.6–1.0)			—		C
Pukkala et al., 1993 Finland (94)	Teacher college alumni	10,038	24	18–22	49	Questionnaire Self-report (LPA)	0.6 (0.4–0.8)			—			C
Terry et al., 1999 Sweden (116)	Swedish Twin Registry	11,659	20.4	Born 1886 – 1925	133	Questionnaire Self-report (LPA)	0.2 (0.3–0.8)			S			C
Zheng et al., 1993 China (136)	Population census 1980–84 Shanghai	1980–84	30+	4	52	Occupational title (OPA)		Energy expenditure (kJ·min) SIR = 80		—		C	

Case-Control Studies	Study Population	Sources of Controls	Age (yr)	Controls (*N*)	Cases (*N*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Dosemeci et al., 1993 Turkey (25)	Hospitals	Hospital based	All	244	49	Occupational title (OPA)		0.5 (0.0–5.0)			NS		C
Goodman et al., 1997 Hawaii (41)	Japanese, Caucasian, Chinese, Hawaiian, Filipino	Population based	18–84	511	332	Questionnaire Interview (LPA, OPA)	0.7	0.9		NS	NS		C
Hirose et al., 1996 Japan (44)	Hospitals	Hospital based	All	26,751	145	Questionnaire Interview (LPA)	0.6 (0.4–0.9)			—			C
Kalandidi et al., 1996 Greece (49)	Athens hospital	Hospital (noncancer)	All	298	145	Questionnaire Interview (LPA, OPA)		Decreased $P = 0.03$			—		C
Levi et al., 1993 Switzerland/Italy (64)	Swiss Canton, Northern Italy hospitals	Hospitals	31–75	572	274	Questionnaire Interview (LPA, OPA)	0.5 (0.3–1.1)	0.7 (0.5–1.0) Household: 0.2 (0.1–0.4)		S	S		C
Olson et al., 1997 USA (88)	New York hospitals	Driver's license Medicare	40–85	631	232	Questionnaire Interview (LPA, OPA)	0.7 (0.4–1.1) At age 16: 0.5 (0.3–0.8)	1.1 (0.6–1.8)		NS NS	NS		C
Shu et al., 1993 China (103)	Shanghai	Population based	18–74	268	268	Questionnaire Interview (LPA, OPA) 20–29, 40–49, 50–59, >60	No effect			—			C
Sturgeon et al., 1993 USA (109)	6 different hospitals	Population based	20–74	297	498	Questionnaire Interview (LPA, OPA)	0.8 (0.5–1.3)	0.5 (0.3–0.8)	0.4 (0.1–1.0)	—	—	—	C

RR, relative risk; CI, confidence interval; LPA, leisure time physical activity; OPA, occupational physical activity; S, significant ($P > 0.05$); NS, nonsignificant; SIR, Standardized Incidence Ratio.

TABLE 5. Studies on physical activity and ovarian cancer risk, dose-response.

Cohort Studies	Study Population	Total (*N*)	Follow-Up Time	Age at Baseline (yr)	Cases (*N*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Mink et al., 1996 USA (81)	Iowa Women Health Study	31,396	7	55–69	97	Questionnaire Self-report (LPA)	2.1 (1.2–3.4)			NS			C
Pukkala et al., 1993 Finland (94)	Teacher college alumni	10,038	24	18–22	51	Occupational Teachers (exercise vs language)	1.7 (0.8–3.2) vs 1.6 (1.1–2.1) No effect			—			C
Zheng et al., 1993 China (136)	Population census 1980–84 Shanghai	Cancer Registry data	1980–84	30+	595	Occupational title (OPA)		Professional vs workers SIR = 132			—		C

Case-Control Study	Study Population	Sources of Controls	Age (yr)	Controls (*N*)	Cases (*N*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Dosemeci et al., 1993 Turkey (25)	Hospital	Hospital based	All	244	49	Occupational title (OPA)		0.3 (0.00–10)			NS		C

RR, relative risk; CI, confidence interval; LPA, leisure time physical activity; OPA, occupational physical activity; NS, nonsignificant; SIR, Standardized Incidence Ratio.

cancer mortality (4,8,16,32,50,52,63,79,89,92,93,107,115, 127), and some contained information on overall cancer incidence (1,19,108). Populations in North America (11 studies), Europe (seven studies), and Asia (one study) were included, and only seven studies included women (Table 1). Taylor and colleagues observed as early as 1962 that sedentary workers were at increased risk of developing cancer compared with active men, indicating the role of occupational physical activity (OPA) in relation to overall cancer risk (115). A significant protective effect of leisure time or OPA was observed in 10 studies (1,8,19, 50,89, 92,107,108, 115,127), whereas six studies suggested a protective effect and one study observed a suggestive increased risk (93) (Table 1). A weaker association between physical activity and cancer mortality, or overall cancer incidence, was reported for women compared with men. An estimation of the effect of leisure time physical activity (LPA) and OPA on overall cancer risk has been performed in a meta-analysis and suggested a 30% independent protective effect of OPA and LPA, respectively, on overall cancer risk for men, with no association for women (101).

A more detailed quantitative description of the volume of physical activity was included in 14 studies (1,4,8,16,19,50, 52,63,79,89,92,107,108,127), and an inverse crude graded dose-response relationship was observed in eight (1,8,19, 50,89,107,108,127) of nine studies in which this was elaborated. Studies in which physical activity was expressed as physical fitness, college athletics, or resting heart rate (8,50) observed a stronger dose-response relationship than those including only self-reported LPA (1) or OPA (108). The observed association between physical activity and overall cancer incidence/mortality in terms of how much physical activity (type, intensity, duration, and frequency) was observed in the Whitehall study was as follows: men who were engaged in regular vigorous activities, e.g., athletics, had a 20% reduction in overall cancer risk compared with sedentary men (107).

Physical Activity and Site-Specific Cancer Risk

Colorectal, colon, and rectal cancer. Physical activity may shorten the fecal transit time and thereby reduce the period of contact between carcinogens and mucosal cells, inducing favorable effects on insulin, prostaglandin, and bile acid levels, which may influence the growth and proliferation of colonic cells.

Cancer of the large bowel is the most frequently investigated cancer in relation to physical activity, and includes at present more than 40,000 colon/colorectal cancer cases in 48 studies (23 cohort studies and 25 case-control studies) conducted in most continents among both sexes (47 studies of men, 28 studies of women) and in different population groups (1,3,5,6,9–11,18,19,25,27,29,35–39,46,51,55,57,58, 60,61,66,69,71,72,74–76,89,91,100,105,106,108,110,113, 114,117,119,123,124,129,130,132,133) (Table 2). The majority of the studies (35 of 48) observe a significant independent protective effect between 10 and 70% on overall colon/colorectal cancer risk (Fig. 2A) for either LPA, OPA,

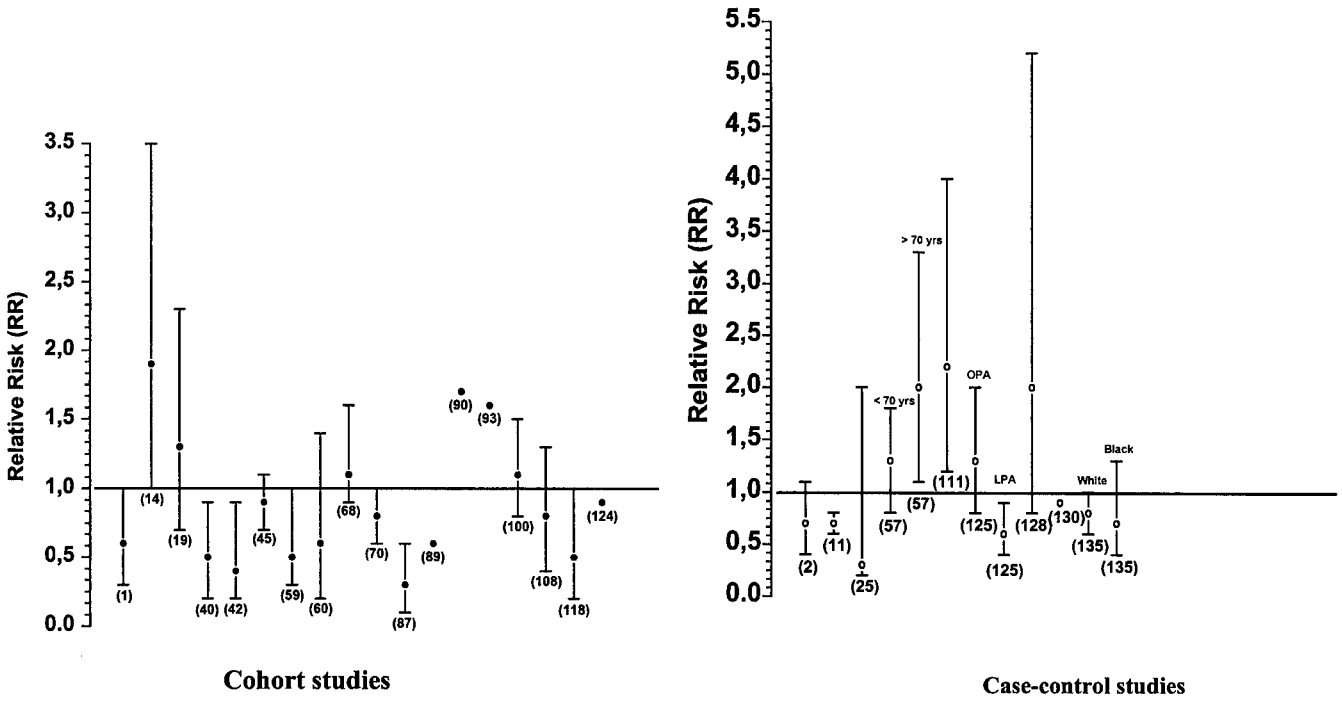


FIGURE 4—Relative risk of prostate cancer with 95% confidence intervals among persons with high versus low physical activity (LPA and OPA) in cohort (●) and case-control studies (○) (see references).

or both activities combined (Fig. 2A). A significant inverse crude graded dose-response association between LPA and colon cancer was observed in 21 (6,10,11,18,19,25,39,57, 66,74,76,91,106,113,114,118,119,124,129,130,132) of 33 observational studies (Table 2, Table 7, and Fig. 2B). When including studies with at least 100 cases, the dose-response associations seems to be especially dependent on moderate-heavy-vigorous physical activity (76) (Fig. 2B). This situation can be illustrated in studies using MET-hours per week (39,76). These observations are demonstrated for both men and women, with a somewhat stronger dose-response relationship for men compared with women (Fig. 2B), without suggesting publication bias (101). Those men and women who reported that more than 1000 kcal·wk^{-1} of energy were expended in vigorous activity through at least three time periods in their lives were observed to have a 40% reduction in colon cancer risk (106). Men who were highly active (energy expenditure of >2500 kcal·wk^{-1} at two assessments) had half the risk of developing colon cancer relative to inactive men (1000 kcal·wk^{-1}). In another study, 21 MET-hours per week were associated with a 50% reduction in colon cancer risk (76) (Fig. 2B), which reflects the fact that approximately 4 h of moderate or 3 h of high-intensity LPA weekly is necessary to reduce colon cancer risk in middle-aged American women. Some studies suggest a greater protective effect on the left than on the right colon (38), and in lean than in obese persons (119), which is also observed to differ by sex (119).

No effect of physical activity related to time period or susceptible period of exposure has been observed. However, lack of influence of physical activity during adulthood (25,72,89) and an increased effect observed for long-term activity in a cohort study (58) suggest that continuous, rather than short-term activity is of importance.

A reduction in bowel transit time because of physical activity may account for the observed effect on colon cancer and the absence of a relationship between physical activity and rectum cancer. In 80% of the 24 studies identified, including 12,055 cancer cases localized in the rectum, no association between physical activity and rectal cancer was observed (Table 2).

Breast, endometrial, and ovarian cancer. Endogenous sex hormones (estradiol, progesterone) are strongly implicated in the etiology of breast and endometrial cancer and possibly also ovarian cancer. Given that physical activity may modulate production, metabolism, and excretion of these hormones, protection against these cancers by means of physical activity is biologically plausible.

Observations from 26 (7, 13, 15, 21, 23, 28, 31, 43, 53, 65, 77, 80, 82, 85, 86, 94, 97, 102, 112, 120, 122, 124, 126, 134) of 41 studies (1, 7, 12, 13, 15, 17, 20–25, 28, 30, 31, 34, 43, 47, 53, 65, 73, 77, 80, 82, 83, 85, 86, 89, 94, 96, 97, 99, 102, 108, 112, 120, 122, 124, 126, 134, 136) including 108,031 breast cancer cases demonstrate that both OPA and LPA are associated with about a 30% reduction in breast cancer risk in pre-, peri-, and postmenopausal women, with a graded dose-response relationship reported in 16 (7,13,21,23,65,77,80,82,85,86,97,99,102,120,122,126) of 28 studies (Table 3 and Fig. 3B). Findings are less consistent than for colon cancer, and the magnitude of the reported associations is generally lower, which may reflect a genuinely weaker relationship. An alternative explanation is that the strength of the physical activity–breast cancer association varies across the lifespan and in subgroups, as it does for more established risk factors (e.g., reproductive factors, body mass index). The actual amount of physical

TABLE 6. Studies on physical activity and prostate cancer risk, dose-response.

Cohort Studies	Study Population	Total (*N*)	Follow-Up Time	Age at Baseline (yr)	Cases (*N*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Albanes et al., 1989 USA (1)	National Health and Nutrition Survey	5141	7–13	25–74	122	Questionnaire Interview (LPA, OPA)	0.8 (0.4–1.4)	0.6 (0.3–1.0)		NS	S		C
Cerhan et al., 1997 USA (14)	Iowa Rural Health Study	3673	12	65–101	71	Questionnaire (LPA)	1.9 (1.0–3.5)			S			C
Clemmesen, 1998 Denmark (19)	Copenhagen male Cohort	5248	15	40–59	113	Questionnaire (LPA)	1.3 (0.7–2.3)			NS			C
Giovannucci et al., 1998 USA (40)	Health professionals	47,542	12	40–75	1362	Questionnaire (LPA)	0.9 (0.8–1.1) MET 0.5 (0.2–0.9)			S			C
Hartman et al., 1998 Finland (42)	Participators (smokers) in a randomized trial (alpha-tocopherol)	29,133	9	50–69	317	Questionnaire (LPA, OPA)			0.4 (0.2–0.9)			S	C
Hsing et al., 1994 China (45)	Shanghai Record linkage 1980–84	Record linkage	1980–84	All	264	Occupational title (OPA)		0.9 (0.7–1.1)			$P = 0.06$		C
Lee et al., 1992 USA (59)	Harvard Health Alumni Study	17,719	26	30–79	419	Questionnaire Self-report (LPA)	0.9 (0.6–1.2) 70+ yr 0.5 (0.3–1.0)			NS NS			C
Lee et al., 1994 USA (60)	Harvard alumni	17,607	26	30–79	454	Questionnaire Self-administered (LPA)	0.6 (0.2–1.4)			NS			C
Liu et al., 2000 USA (68)	Physician Health Study	22,071	11.1	40–84	982	Questionnaire Self-administered (LPA)	1.1 (0.9–1.4)			NS			C
Lund Nilsen et al., 2000 Norway (70)	Men	22,895	9.3	40+	644	Questionnaire Self-report (LPA)	0.8 (0.6–1.0)			NS			C
Oliveria et al., 1996 USA (87)	Texas	12,975	1–19	20–80	94	Questionnaire Fitness (LPA)	0.26 (0.1–0.6)			S			C
Paffenbarger et al., 1987 USA (89)	San Francisco longshoremen Harvard college	6351 51,977	12–22 12–22	35–74 35–70	30 (Fatal) 154	Occupation (OPA) Questionnaire	0.65 0.6 ($P < 0.05$)			—			C
Paffenbarger et al., 1992 USA (90)	Students	17,719	26	28–58	154	Questionnaire Self-administered (LPA)	1.66			—			C
Polednak et al., 1976 USA (93)	Retrospective cohort Death certificate	8393			156	College athletics	1.64			—			C
Severson et al., 1989 Hawaii (100)	Japanese men on Hawaii	M 8006	18–21	46–68	206	Questionnaire Self-administered (LPA, OPA) Resting heart rate	1.1 (0.8–1.5) 1.0 (0.7–1.4)			NS NS			C
Steenland et al., 1995 USA (108)	National Health and Nutrition Survey			25–74	156	Questionnaire (LPA, OPA)		0.8 (0.4–1.3)		—	—		C
Thune and Lund, 1994 Norway (118)	Men	53,242	16.3	19–50	220	Questionnaire Self-report (LPA, OPA)			0.5 (0.2–1.0)			S	C
Vena et al., 1987 USA (124)	Washington	430,000	1950–79	All	8116 (Fatal)	Occupational title		0.93 ($P < 0.05$)			—		C

TABLE 6. *Continued*

Case-Control Studies	Study Population	Sources of Controls	Age (yr)	Controls (*M*)	Cases (*M*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Andersson et al., 1995 Sweden (2)	Hospital	Population based	<80	252	256	Questionnaire	0.7 (0.4–1.1)			NS			C
Brownson et al., 1991 USA (11)	White Missouri Cancer Registry	Other cancer cases at the registry	>20	14,269	2878	Occupational title (OPA)		0.7 (0.6–0.8)			S		C
Dosemeci et al., 1993 Turkey (25)	Hospital	Hospital based	All	2127	27	Occupational title (OPA)		0.3 (0.0–2.0)			NS		C
Ilic et al., 1996 Serbia (48)	Hospital patients	Noncancer hospital patient		101	202	Occupation (OPA)		3.9 (2.1–7.2)			—		
Le Marchand et al., 1991 USA (56)	Hawaii Tumor Registry	Population	—	899	452	Questionnaire Interview (OPA)		>70 yr: 0.5 (0.3–0.9)			S		C
Sung et al., 1999 Taiwan (111)	Hospital in Taipei	Hospitals	—	180	90	Questionnaire Interview (LPA, OPA)	2.2 (1.2–4.0)			—			C
Villeneuve et al., 1999 Canada (125)	Multicentre (NCEES project)	Population	50–74	1623	1623	Questionnaire Self-report (LPA, OPA)	Midteens: 1.3 (0.8–2.0) 2 yr before: 0.7 (0.4–1.4)	Midteens: 0.6 (0.4–0.9) 2 yr before: 0.9 (0.5–1.6)		NS NS	NS NS		C
West et al., 1991 USA (128)	Utah Cancer Registry	Population	45–74	679	358	Questionnaire Interview (LPA)	2.0 (0.8–5.2)			—			C
Whittemore et al., 1995 USA (131)	U.S. and Canadian Cancer Registry	Population	<84	1655	1645	Questionnaire Interview (LPA)	No effect			NS			C
Yu et al., 1988 USA (135)	Hospital	Cancer and noncancer hospital	—	3124	1162	Questionnaire Interview (LPA)	White: 0.8 (0.6–1.0) Black: 0.7 (0.4–1.3)			S S			C

RR, relative risk; CI, confidence interval; LPA, leisure time physical activity; OPA, occupational physical activity; S, significant ($P > 0.05$); NS, nonsignificant; MET, metabolic equivalent.

TABLE 7. Studies on physical activity and testicular cancer risk, dose-response.

Cohort Studies	Study Population	Total (*N*)	Follow-Up Time	Age at Baseline	Cases (*N*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Paffenbarger et al., 1992 USA (90)	Students	56,583	28.62		45	College athletics	1.2 ($P = 0.6$)			—			C
Thune and Lund, 1994 Norway (118)	General population	53,242	16.3	19–50	47	Questionnaire Self-report (LPA, OPA)			2.0 (0.6–6.9)			NS	C

Case-Control Studies	Study Population	Sources of Controls	Age (yr)	Controls (*N*)	Cases (*N*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Brownson et al., 1991 USA (11)	White Missouri Cancer Registry	Other cancer cases at the registry	>20	16,895	252	Occupational title (OPA)		0.5 (0.3–0.8)			S		C
Dosemeci et al., 1993 Turkey (25)	Hospital	Hospital based	All	2127	191	Occupational (OPA) Energy expenditure Sitting time		1.0 (0.6–2.0) 1.4 (0.7–2.5)			NS		C
Forman et al., 1994 UK (26)	England, Wales	General practitioners	15–49	794	794	Questionnaire (LPA, OPA)	0.5 (0.3–0.9)			S			C
Gallagher et al., 1995 Canada (33)	Cancer Registries Alberta, BC	Medicare Driver's license	15–79	996	510	Questionnaire 24 h (LPA, OPA)	0.7 (0.5–0.9)	0.9 (0.6–1.3)		S			C
Scrivastava et al., 2000 Canada (98)	Ontario Cancer Registry	Ontario Ministry of Finance Property	All	251	212	Questionnaire (LPA, OPA) Activity in teens	2.6 (1.1–5.9)			—			C

RR, relative risk; CI, confidence interval; LPA, leisure time physical activity; OPA, occupational physical activity; S, significant ($P > 0.05$); NS, nonsignificant.

activity that is needed to reduce breast cancer risk has in several studies been reported as leisure time physical activity for at least 4 h·wk^{-1} (7,97,120) of at least moderate intensity (4–5 MET) (126) or continuous vigorous activity (24.5 MET-h·wk^{-1}) (13). A dose-response relationship was especially observed in case-control studies in where MET-hours per week was assessed (Fig. 3B). LPA during puberty (73,126) may be particularly important for reducing breast cancer risk. However, continuous high levels of LPA throughout life may be just as important as physical activity in puberty (28,73,126).

Of 12 studies (25,41,44,49,64,84,88,94,103,109,116,136) of populations in North America, Europe, and Asia, a link between physical activity and endometrial cancer risk was observed in 8 studies (44,49,64,84,88,94,109,116), with a significant (20–80%) reduced risk of endometrial cancer (Table 4). A graded dose-response association was observed in two studies (64,116). In a cohort study, hard LPA was observed to reduce endometrial cancer by 80%, whereas occasional exercise gave the same risk reduction as at least three to four times per week in another study (44). Occupational physical activity appeared to be protective only among women aged 50–69 yr (84).

Only four studies (25,81,94,136) have been identified that focus on the association between physical activity and ovarian cancer. One study has observed a significant increased risk attributable to high LPA (81), whereas others have observed a decreased risk (136), but no dose-response relationship has been demonstrated (Table 5).

Prostate and testicular cancer. The observation that athletes display lower levels of circulating testosterone than nonathletes, and the role of testosterone in relation to prostate and testicular cancer, has led to the hypothesis that physical activity might protect against the development of these two cancer types. However, trauma in sports may be hypothesized to increase testicular cancer risk (121).

Of 28 published studies (1, 2, 11, 14, 19, 25, 40, 42, 45, 48, 56, 59, 60, 68, 70, 87, 89, 90, 93, 100, 108, 111, 118, 124, 125, 128, 131, 135) including 22,521 prostate cancer patients in North America, Asia, and Europe, 14 studies (1, 2, 11, 14, 40, 42, 60, 70, 89,90,118,124,125,135) demonstrated that either OPA or LPA, or both activities combined, significantly decreased prostate cancer risk by 10–70%, but an inverse graded dose-response association was only observed in 10 of 19 studies (Fig. 4 and Table 6). In one study, at least 12 kJ·min^{-1} for occupational activity was required for a reduction in prostate cancer risk (45). Men who expended at least 1000 kcal·wk^{-1} and up to 3000 kcal·wk^{-1} had at most a 70% reduction in risk. However, the data are inconsistent, as three studies observed a significantly increased risk among physically active men (14,48,56). These studies related to prostate cancer are hampered by variation in detection of latent disease.

Data for testicular cancer show the same discrepancies as for prostate cancer (11,25,26,33,90,98,118), with a recent study observing an increased risk among physically active men (98), which contrasts with the U.K. testicular group's findings that suggest a decreased risk (26). Three of five studies observed a graded inverse dose-response relationship (Table 7).

TABLE 8. Studies on physical activity and lung cancer risk, dose-response.

Cohort Studies	Study Population	Total (*N*)	Follow-Up Time	Age at Baseline	Cases (*N*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Albanes et al., 1989 USA (1)	National Health and Nutrition Survey	M 5141	7–13	25–74	114	Questionnaire Interview (LPA, OPA)		0.5 (0.3–0.8)			S		C
Clemmesen, 1998 Denmark (19)	Copenhagen male Cohort	M 5248	15	40–59	226	Questionnaire (LPA)	0.8 (0.6–1.1)			NS			C
Lee and Paffenbarger, 1994 USA (60)	Harvard alumni	M 17,607	26	30–79	57	Questionnaire (LPA)	0.4 (0.2–0.9)			S			C
Lee et al., 1999 USA (62)	Harvard alumni	M 13,905	15		245	Questionnaire Self-report (LPA)	0.6 (0.4–1.0)			S			C
Paffenbarger et al., 1987 USA (89)	San Francisco longshoremen Harvard College	M 6351	12–22	35–74	112 (Fatal)	Occupational title (OPA)	0.6			—			C
Paffenbarger et al., 1992 USA (90)	Students	M + F 56,583	12–22	28–58	194	College athletics	1.2 ($P = 0.3$)			—			C
Severson et al., 1989 USA (100)	Japanese men	M 8006	18–21	46–68	194	Questionnaire 24 h (LPA, OPA)			0.7 (0.5–1.0)			S	C
Steenland et al., 1995 USA (108)	National Health and Nutrition Survey	M + F 14,407		25–74	15159	Questionnaire (LPA, OPA)		M: 0.8 (0.4–1.4) F: 0.7 (1.7–0.6)			NS NS		C
Thune and Lund, 1997 Norway (121)	General population	M 53,242	16.3	19–50	413	Questionnaire Self-report (LPA, OPA)	Tot: 0.4 (0.2–0.9) Small cell: 0.4 (0.6–0.9)		M: 0.7 (0.5–1.0)	S S		S NS	C
		F 28,274			51		—		F: 0.9 (0.2–3.6)				

Case-Control Studies	Study Population	Sources of Controls	Age (yr)	Controls (*N*)	Cases (*N*)	Physical Activity Assessment	RR (95% CI) Highest vs Lowest Physical Activity			Dose-Response			Evidence Category
							LPA	OPA	Total	LPA	OPA	Total	
Brownson et al., 1991 USA (11)	White Missouri Cancer Registry	Other cancer cases at the registry	>20	M14,269	4700	Occupational title (OPA)		0.8 (0.6–0.9)			S		C
Dosemeci et al., 1993 Turkey (25)	Hospital	Hospital based	All	M 2127	1148	Occupational title (OPA)		1.0 (0.8–1.3)			NS		C

RR, relative risk; CI, confidence interval; LPA, leisure time physical activity; OPA, occupational physical activity; S, significant ($P > 0.05$); NS, nonsignificant; M, males; F, females.

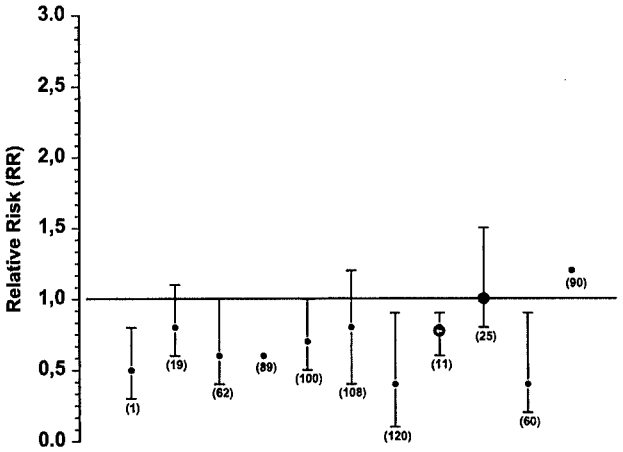


FIGURE 5—Relative risk of lung cancer with 95% confidence intervals among persons with high versus low physical activity (LPA and OPA) in cohort (●) and case-control (○) studies.

Lung cancer. It is well established that physical activity improves ventilation and perfusion, which may in turn reduce both the concentration of carcinogenic agents in the airways and the duration of agent–airway interaction. However, the association of physical activity with lung cancer has only been elaborated in 11 studies (1, 11, 19, 25, 60, 62, 89,90,100,108,121) including 7,726 men and women, and most of these studies were conducted in men only (Table 8). Findings from 6 (1,11,60,62,100,121) of these 11 studies (five cohort studies and one case-control study) support a protective effect of both LPA and OPA of 20–60%, with an inverse graded dose-response relationship (Fig. 5). No studies suggested an increased risk attributable to physical activity. These studies indicate that a continuous 4 $h \cdot wk^{-1}$ of hard leisure time activity in order to keep fit (121), and participation in activities of at least moderate activity (>4–5 MET), but not light activity (<4–5 MET) (62), reduced the lung cancer risk independently after careful adjustments for smoking and other possible risk factors. An effect of physical activity related differently to various histologic types of lung cancer has also been observed (121).

Others. A small number of studies have elaborated on the effect of physical activity on renal cancer, bladder cancer, stomach cancer, malignant melanoma, brain tumors, and malignant tumors in the lymphatic and hematopoietic tissues (19,25,31,78,89,93,94,100). No clear patterns can be drawn from these studies (see Table 9).

FUTURE RESEARCH ISSUES

When considering the research field of physical activity and cancer, five different research issues can be delineated.

1. The lack of understanding of the biological mechanisms operating between physical activity and site-specific cancer risk warrants further studies.
2. Assessing biomarkers, intermediate steps, and precancerous lesions for site-specific cancer may give us further insight into the relationship between physical activity and cancer that will be of particular interest for public health recommendations.

TABLE 9. Summary for site-specific cancer, type of studies, dose-response.

Cancer Site	No. of Studies			Cases (*N*)	Adjustments Confounding	Association Overall (High vs Low)			Physical Activity Assessments (Type, Intensity, Frequency, Duration, Time)	Characteristics Disease	Dose-Response		
	Total	Cohort	Case-Control			No	Positive	Negative			No	Positive	Negative
Colorectal Colon	48	23	25	40,674	Diet, BMI, Family history	13	0	35 17 cohort 18 case-control	30 studies on LPA 37 studies on OPA intensity; categories, MET	Gender differences Proximal and distal location?	14	—	21
Rectal	24	9	15	12,055	Diet, BMI	17	1	6 1 cohort 5 case-control	13 studies on LPA 22 studies on OPA		4	—	2
Breast	41	18	23	108,031	Menopausal status, parity, BMI, diet, exogeneous hormone (HRT, OC)	15	0	26 12 cohort 14 case-control	32 studies on LPA 19 studies on OPA intensity; categories, MET	Menopausal status Carcinoma in situ	19	—	16
Endometrial	12	4	8	14,909	Parity, BMI, exogeneous hormones (HRT)	4	0	8 3 cohort 5 case-control	9 studies on LPA 9 studies on OPA intensity; categories, MET	Histology?	2	—	3
Ovarian	4	3	1	792	Family history, BMI, exogenous hormones	2	1	1 1 case-control	1 studies on LPA 3 studies on OPA	Histology	4	1	0
Prostate	28	18	10	22,727	Family history, BMI, diet, alcohol	12	3	13 9 cohort 4 case-control	18 studies on LPA 13 studies on OPA intensity; categories, MET	Latency of disease	8	1	10
Testicular	7	2	5	2051	Cryptorchidism, hernia inguinalis, family history, BMI	3	1	3 0 cohort 3 case-control	5 studies on LPA 6 studies on OPA	Histology	1	1	3
Lung	11	9	2	7164	Smoking, diet, family history	5	—	6 5 cohort 1 case-control	7 studies on LPA 6 studies on OPA long-term activity	Histology	5	—	6

LPA, leisure time physical activity; OPA, occupational physical activity; BMI, body mass index; MET, metabolic equivalent.

3. Improving the quality of physical activity assessment methods is one of the most important methodological issues in the field of research on physical activity and cancer risk. This includes measurements of all types and components of physical activity across the entire lifetime, with attention to susceptible periods, gender, age, cultural, and individual variations.
4. The importance of genetic predisposition to be physically active combined with the knowledge that cancer is a genetic localized disease warrants studies in general populations and high-risk groups alike. This is especially important when considering the improved insights into cellular and molecular levels in the development of malignancy.
5. Controlled randomized clinical trials studying the physical activity–cancer association in relation to biological mechanisms and biomarkers or intermediate steps and cancer types are warranted. Thus, through such studies alternative explanations for the apparent protective effect of this exposure against some cancers can be better explored in relation to confounding factors.

Consequently, discrepancies between studies elaborating the association between physical activity and site-specific cancer risk may be explained by real differences or lack of information on the various components. These components may consist of physical activity (type, intensity, duration), incomplete information about the cancer type studied (localization, histologic type) combined with incomplete understanding of the pathogenesis of most cancer and lack of knowledge regarding possible biological mechanisms operating between physical activity and cancer.

CONCLUSION: CURRENT EVIDENCE AND RESEARCH ISSUES

How should the physician understand and interpret our existing knowledge of the association between physical activity and cancer? Although existing studies are hampered by methodological limitations, the totality of the evidence confirms a protective effect of physical activity with a graded dose-response relationship between physical activity and cancers of the colon and also of the breast, whereas no association has been observed with cancer of the rectum. Further data concerning cancer of other organ cancers are required. Notably, no consistently increased risk has been observed for any cancer type. This emerging knowledge is especially important when considering the observed overall increase in physical inactivity in westernized countries across the lifespan. The optimal permutation of intensity, duration, and frequency of physical activity across the lifespan is unclear, but it is gender, age, and site specific. We need further insight into these dimensions of physical activity, as well as studies of biological mechanisms, biomarkers, and intermediate steps, in order to understand in more detail how physical activity reduces cancer risk.

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Dose-response of physical activity and low back pain, osteoarthritis, and osteoporosis

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ABSTRACT

VUORI, I. M. Dose-response of physical activity and low back pain, osteoarthritis, and osteoporosis. *Med. Sci. Sports Exerc.,* Vol. 33, No. 6, Suppl., 2001, pp. S551–S586. **Purpose:** The purpose of this study was to examine the evidence for causal relationships between physical activity (PA) and low back pain (LBP), osteoarthritis (OA), and osteoporosis (OP), and for dose-response relations involved. **Methods:** Computer database searches and personal retrieval systems were used to locate relevant literature. **Results:** PA can be effective in preventing LBP (Category A) but prolonged, heavy loading can lead to LBP (Category C). Specific exercises have not been found effective in treatment of acute LBP (Category A), but PA can be effective in chronic LBP (Category B), especially for diminishing the effects of deconditioning. No evidence indicates that PA directly prevents OA. Large amounts of intensive PA involving high impacts or torsional loadings or causing injuries increases risk of OA (Category C). Light or moderate PA does not increase the risk of OA (Category C). PA can be effective in the treatment and rehabilitation of OA (Category B). High-intensity loading is osteogenic and possibly useful in prevention of OP (Category A) at the loaded site, but low to moderate loading is not osteogenic (Category D). Static efforts and slow movements are ineffective or less effective than fast application of force (Category B). The types of PA to attain the effects mentioned above are known except in the case of prevention of LBP, but dose-response relationships are poorly known; at best, semiquantitatively on the basis of just a few studies. **Conclusion:** Given the shown primary and/or secondary preventative effectiveness of PA regarding LBP, OA, and OP, research to elucidate the inadequately known dose-response relations should be given high priority. **Key Words:** PHYSICAL ACTIVITY, EXERCISE, SPORT, LOW BACK PAIN, OSTEOARTHRITIS, OSTEOPOROSIS, PREVENTION, TREATMENT, DOSE-RESPONSE, REVIEW

Low back pain (LBP), osteoarthritis (OA), and osteoporosis (OP) are prevalent and increasing musculoskeletal disorders that cause a great amount of suffering, loss of productivity and independence, as well as costs to individuals and societies. The prevalence of all these conditions is increasing, partly because of aging of populations and partly because of widespread adverse changes in lifestyles and environments. There is increasing evidence that physical activity is related to the development and course of these conditions, but the relationships of causality, directions, strength, and modifying factors are only partially known. However, in order to advise people and to engineer work, leisure, domestic chores, and environments regarding physical activity for the best of health, thorough knowledge of the effects on health of various forms of physical activity and of the dose-response relationships involved is needed. In this article, the published literature on the relationships between physical activity (PA) and LBP, OA, and OP is reviewed focusing primarily on the question, How much and what kind of PA (dose, exposure) cause development, prevent development, or prevent worsening of LBP, OA, and OP? The primary interest is on the effects of leisure time physical activity (LTPA) in apparently healthy individuals.

The analysis is conducted in the following successive steps: examination of the evidence for 1) the existence of one or more of the possible relationships; 2) causality of the relationships; 3) mechanisms of the effects; 4) characteristics of PA causing a given health outcome; 5) possibilities to assess and quantitate the dose or exposure; 6) analysis of published studies regarding dose-response relationships; 7) descriptive and quantitative conclusions; and 8) recommendations for further research.

The analysis is derived mainly from human studies. Information from experimental studies on animals is used especially to obtain firm evidence of the existence of a relationship, its causality and mechanism, and the characteristics of the activity causing the outcome.

METHODS

The material was collected by a computerized literature search of the MEDLINE/PubMed, and DataStar, SPORT, and the Cochrane database from 1990 to July 2000 to identify human studies on relationships between PA and LBP, OA, and OP. The key words were exercise, exercise therapy, physical education and training, physical activity, physical fitness, and sport connected with dose-response, level, volume, quantity, amount, dose, effect, and impact or influence of PA/exercise. In addition, bibliographies of major reviews published in peer-reviewed journals and major textbooks as well as in part of the original publications were

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cross-referenced and the author's own archives were used especially to identify studies published before 1990. Special emphasis was paid to identify randomized (RCT) and other controlled (CT) trials. Relevant articles derived from title and abstract were copied for review.

The computerized searches yielded the following results. The DataStar search found 330 articles on LBP, 327 on OA, and 524 on OP. The PubMed search revealed 29 reviews, 45 controlled trials, and 78 other studies on LBP. The corresponding figures for OA were 18, 20, and 45, and for OP 50, 18, and 70. The search of the Sport database revealed 14 articles on LBP, 30 on OA, and 72 on OP. A substantial part of the publications identified by the three searches were the same. The search of the Cochrane Library on LBP revealed 180 studies in the controlled trials registers and 30 completed systematic reviews. The corresponding figures for OA were 76 and 16, and for OP, 77 and 16.

RESULTS

LBP

Background. LBP is pain, muscle tension, or stiffness localized below the costal margin and above the inferior gluteal folds, with or without leg pain (sciatica). It may be acute (aLBP) or chronic (persisting 12 wk or more) (cLBP). Nonspecific LBP is that not attributed to recognizable pathology, such as infection, inflammation, rheumatoid arthritis, fracture, tumor, or OP. LBP is nonspecific in about 85% of people. The origin and mechanisms of the pain are not definitely known.

Risk factors for LBP are poorly understood: the most frequently reported are heavy physical work; frequent bending, twisting, lifting, pulling, and pushing; repetitive work; static postures; and vibrations. Psychosocial risk factors include anxiety, depression, job dissatisfaction, and mental stress at work. Several risk factors related to inactivity or immobilization have been proposed: reduced muscle strength in back, abdominal, and thigh muscles; reduced endurance in back muscles; hypermobility in lumbar column; and hypomobility of hip joints (96). Genetics is likely to play a significant role in the development of the processes leading to LBP (9).

PA might relate to LBP as a provoking, preventing, worsening, or improving factor. The theoretical rationale for these relations includes the following ideas, derived from the summary of Suni (234): 1) PA can induce acute and repetitive subclinical or more severe injuries in the back structures; 2) higher strength of the muscles of the back and trunk could protect the back from injury or minimize the effects of injurious events; 3) higher endurance of the trunk muscles helps to maintain motor control because of less fatigue in various tasks thus decreasing the risk of high loading of spine structures or occurrence of malfunctions and consequently development of injury; 4) better flexibility may decrease the risk of injury especially during lifting and bending activities; 5) good motor skills decrease the risk of injury in various tasks; and 6) good general or aerobic endurance helps to counteract fatigue and development of injury. Additional suggested mechanisms include improved circulation to the back structures and improved mood, which would influence favorably sensitivity to pain (233).

In addition, PA may influence the development or the course of an LBP episode in indirect, unspecific ways, e.g., through influences on body mass, mood, perceptions, and motivation, and by decreasing or abolishing the effects of physiological deconditioning because of inactivity or hypoactivity. Current knowledge of the risk factors, genesis, and mechanisms of action of PA in relation to LBP provide only a weak theoretical basis to search for dose-response relationships between PA and prevention, causation, treatment, and secondary prevention of LBP.

Review of research evidence. In the following review, the examination of evidence for associations between PA and LBP is mainly limited to LTPA and to low back symptoms and clinical findings. Thus, occupational activities, results of various fitness tests, and consequences of LBP such as absence from work are not thoroughly considered.

LTPA and incidence of LBP. Physical activity may have dual roles as positive and negative influences on the back (252). One case-control study (174) did not find increased risk of lumbar herniation attributable to sports and weight lifting, and a population-based prospective cohort study with 1-yr follow-up on 2715 adults (41) did not find increased or decreased risk of LBP associated with most types of LTPA, although home-improvement work in men and regular sport in women increased the risk. Increased risk of developing low back problems and pathology associated with long-term heavy physical loading is supported by studies on workers (205,233,251). A recent cross-sectional study on a large population sample revealed that activities characterized by an awkward posture, by maintaining the posture for a long time, or by often bending or rotating the trunk increased the risk of LBP, with odds ratios between 1.1 and 1.6. More than 13% of the 1-yr prevalence of LBP could be attributed to these activities (196). Three prospective longitudinal population-based studies did not find any relationship between LTPA and development of LBP (5,78,130), but among industrial workers, low levels of LTPA were predictive of development of LBP during 5-yr follow-up (143). A recent systematic review (233) of RCTs as well as earlier reviews on the topic concluded that there is convincing evidence that exercise training can be effective and is currently the only effective tested modality for prevention of LBP. One recent RCT (93) not included in the review cited above found no differences in LBP episodes at 6, 12, or 24 months in previously asymptomatic subjects with weak abdominal muscle strength after participation in either back education or back education plus abdominal exercise instruction group. Summary of the reviewed RCTs is presented in Table 1.

In conclusion, there is strong evidence (Category A) that LTPA can have a primary preventive effect on LBP. Most forms of LTPA as commonly practiced do not seem to increase the risk of LBP. Prolonged heavy occupa-

TABLE 1. RCTs on prevention of LBP by PA.

Reference	Subjects: N	Subjects: Age	Subjects: Sex	Subjects: Population	Physical Activity	Results	Comment
Donchin et al., 1990 (50)	CAL = 46 BS = 46 C = 50	45 48 45	Men: 37% Men: 35% Men: 30%	Hospital employees, at least 3 annual episodes of LBP	CAL: calisthenics to strengthen abdominal muscles to expand spinal forward flexion and rectifying general posture; supervised sessions 45 min, 2×/wk, 3 mo BS: back school (instruction, advice), 5 sessions 12 mo, 90 min C: control group, no measures	Monthly surveillance over 1 yr showed significantly less "painful months" in CAL (4.5) as compared with BS (7.3) and C (7.4). Significantly larger increase in trunk forward flexion and abdominal muscle strength in CAL as compared with BS and C.	
Gundevall et al., 1993 (76)	T = 28 C = 32	38 37	Men: 1 (of all subjects)	Personnel at a geriatric hospital, with or without back symptoms	T: individual exercise sessions 5 times by physiotherapist, exercises to increase dynamic endurance, isometric strength and functional coordination of trunk muscles performed during working hours, in average 6×/mo, 20 min, during 13 mo C: no measures	Absence because of LBP: 28 day/1 prs in T, 155 days/ 12 prs in C ($P < 0.004$). Days with complaints: 54 in T, 94 in C ($P < 0.02$). Significant increase of back muscle strength in T vs C. Significant increase of back muscle strength in T vs C.	
Helewa et al., 1999 (40)	T+BE = 203 BE = 199	38 38	Men: 46% Men: 47%	City residents, employees, and students of academic and medical institutions, asymptomatic and with weak abdominal muscle strength	T+BE: T: physiotherapist instructed individually simple exercises to be performed daily at home BE: one 90-min class given by a physiotherapist at baseline and at 1 and 2 yr.	No significant differences between the groups in LBP episodes at 6, 12, or 24 mo. No improvement of abdominal muscle strength in T+BE.	Poor compliance: loss to follow-up 36% in T+BE, 17% in BE
Kellet et al., 1991 (110)	T = 58 C = 53	41 (for 37) 42 (for 48)	Men: 70% Men: 70%	Employees of one large industrial firm, with or without current LBP, willing for training	T: duration 1½ years; supervised session 1×/wk during working hours, 30–35 min exercises for flexibility, strength, endurance, and coordination and in one third of the classes back education for 10 min; in addition, at least 30 min endurance activity 1×/wk C: control group, no measures	In T, 50% and 51% decrease of episodes of LBP and sick days because of LBP during 1½-yr intervention period compared with respective data during the 1½ years prior to the intervention. In C, the corresponding percentage changes were 58% increase in LBP episodes and 65% increase in sick days because of LBP. The differences between the groups are significant.	36% of the subjects in T lost from follow-up
Linton et al., 1989 (147)	T = 36 C = 30	20–59	Men: 0	Nursing personnel with a history of intermittent LBP during the 2 yr prior to the study	T: 5-wk program at a rehabilitation clinic, 4 h of aerobic activities and 4 h of back education daily C: control group, no measures	At 6 mo, subjects in group T reported greater improvements than C subjects in pain, fatigue, and activities of daily living. At 18 mo, sick days for T had increased from baseline.	Individual contribution of each intervention to the positive results is unclear
Linton et al., 1996 (148)	T = 36 C = 32	42 42	Men: 31% Men: 28%	Employees of tobacco and distribution companies, LBP during preceeding year, otherwise healthy, sedentary	T: individually planned training C: training instructions, free admission to gym	No difference in LBP between the groups.	

tional and sports activities seem to increase the risk of LBP, but the role of subclinical or more severe injuries cannot be completely excluded. At the other end of the PA spectrum, a systematic, critical review of the current literature did not find support for the popular opinion that sitting while at work is associated with increased risk of LBP (84). Concerning dose-response issues, the available evidence suggests that most commonly practiced LTPA activities are safe in terms of LBP within a broad range of volume and intensity. For primary prevention of LBP the possibly effective characteristics of LTPA have not been verified, and therefore dose-response relationships are not known either.

LTPA in secondary prevention. Several reviews have examined the effects of exercise training and LTPA in the treatment and secondary prevention of aLBP and cLBP (16,26,28,61,96,121,131,249,259). The most recent review of RCTs (until February 2000, $N = 39$) (250) presents the

current evidence using a rigorous protocol of data collection and analysis. The conclusions are as follows:

For aLBP. Strong evidence (Category A) indicates that exercise therapy is not more effective than inactive treatments or other active treatments. Flexion and extension exercises are not effective. Sound evidence is lacking to confirm the claim that exercises in aLBP may prevent future recurrences or chronicity. Low stress activities such as walking, biking, or swimming can be started during the first 2 wk.

For cLBP. 1) Exercise versus other active treatment: strong evidence (Category A) indicates that exercise therapy and conventional physiotherapy are equally effective and that exercise therapy is more effective than usual care by a general practitioner. Limited evidence (Category C) suggests that exercise provides better outcomes than back school. 2) Exercise therapy versus inactive or "placebo" treatment: the evidence is conflicting (Category C) regarding the effectiveness of exercise therapy for cLBP. 3) There is conflicting evidence (Category C) about which type of exercises, extension or flexion, are more effective. 4) Strong evidence (Category A) indicates that strengthening exercises are more effective than other types of exercise. The evidence is conflicting that strengthening exercises are more effective than inactive treatment (Category C).

The reviewers conclude that specific exercises are not recommended for patients with aLBP or cLBP. However, exercises may be useful within an active rehabilitation program if they facilitate and precipitate increasing ordinary activity and returning to work. Pertinent data of the reviewed studies are presented in Table 2.

Another recent systematic literature review of 16 RCTs (all included in van Tulder et al. (250)) (233) essentially agrees with the above-cited conclusions by stating that in aLBP various forms of exercise training are ineffective treatment modalities (Category A), and in cLBP exercise training is effective in decreasing pain (Category A).

Some studies from 1999–2000 not included in the cited reviews are worth reviewing. One RCT found that endurance training of trunk extensor muscles for 6 wk in subjects with subacute LBP decreased symptoms and improved function at 3 wk but not at 6 wk in the training group as compared with the control group (34). This study thus suggests that endurance training of the trunk muscles expedites the recovery process for patients with an acute episode of LBP.

Another RCT on subjects with cLBP found that an individually adjusted exercise program specially designed to train trunk muscle function (endurance) and coordination decreased back pain intensity and self-reported functional disability in the treated group more than in the placebo-treated subjects at 6- and 12-month follow-up (105).

Mannion et al. (160) compared the efficacy of modern active physiotherapy, muscle reconditioning on training devices, and low-impact aerobics for cLBP in a randomized trial. All three treatments proved to be equally efficacious in reducing symptoms and disability in tasks of daily living immediately after the therapies and during the following 6 months. The equal results in the three groups suggest that the effects were not reduced through specific physiologic adaptations but rather through some "central" psychological mechanism(s). Essential information of the three studies cited above is included in Table 2.

Dose-response relationship could be directly examined in one study only (158). In this CT, intensive as compared with light intensity back strengthening program resulted in significantly better improvement in a combined pain, disability, and impairment index at 3- and 9-month follow-up. In another CT (159), the "dose" in two exercise programs differed in the degree of flexion in dynamic exercises and in including or excluding hyperextension. LBP rating improved more in the group that used wider flexion and hyperextension in the exercises at 3 but not at 12 months. No subgroup analyses were reported in the published studies on dose-response issues. Comparison of different studies regarding dose-response relationships is not warranted or even possible because of wide differences in a number of factors that influence the results.

Concluding remarks. The current evidence of the role of PA in causation and primary and secondary prevention of LPB can be summarized as follows.

1. Prolonged, repetitive, heavy physical activity at work or in sports can cause LBP in susceptible individuals (Category C), but the role of injury is not known. No dose-response relationships have been established and, because of the large variation of individual susceptibility and to the multiple physical, physiological, psychological, and social factors involved, it is likely that only crude, categorical dose-response relationships can be established.
2. Strong evidence (Category A) indicates that PA can have a preventive effect on LBP. The characteristics of effective activity have not been established. However, it is worth noting that trunk extensor endurance was systematically associated with LBP in cross-sectional studies (234), and it had predictive value for first-time LBP in two population studies (16,153), and endurance training of trunk muscles showed positive results in two RCTs on secondary prevention of LBP (34,105).
3. Strong evidence (Category A) shows that specific exercises are not effective in the treatment of acute LBP, but continuing ordinary activities and starting low-stress aerobic activities during the first 2 wk is indicated in order to improve recovery and lessen disability.
4. The role of PA in the treatment and secondary prevention of cLBP should be examined from at least two points of view: first, symptoms and psychosocial consequences; and second, biological effects of prolonged deconditioning. Some evidence (Category B) suggests that PA, especially as structured exercises, alleviates symptoms of cLBP and may improve function. These

TABLE 2. RCTs on the effectiveness of exercise training as treatment/rehabilitation of LBP.

Reference	Subjects: N	Subjects: Age	Subjects: Sex	Subjects: Group	Exercise Training	Results	Comment
Bentsen et al., 1997 (13)	T1 = 41 T2 = 33	57	F	Chronic nonspecific LBP	T1: home, back and abdominal strengthening exercises, 10×/d, 12 mo + fitness center, dynamic exercises, 2×/wk, 30 min, 3 mo T2: home only, as above	T1 more improved in functional status after 12 mo.	Data poorly presented.
Bronfort et al., 1996 (23)	T1 = 71 T2 = 71 R = 71	20–60	F, M	Chronic nonspecific LBP	T1: strengthening exercises for trunk, legs, 20 reps each, 20 sessions, 11 weeks + manipulative therapy T2: stretching + manipulative therapy, 20 1-h sessions, 11 wk R: strengthening exercises as in T, + NSAIDs	No significant differences in pain, functional status, or generic health after 5 and 11 wk between the groups.	
Buswell, 1982 (25)	T1 = 25 T2 = 25	16–59	F, M	Chronic recurrent LBP	T1: flexion exercises, 8–14 times T2: extension exercises, 8–14 times	No difference in change of pain between the groups.	Data incompletely presented.
Cherkin et al., 1998 (32)	T = 133 R = 122 R2 = 66	20–64	F, M	Acute LBP	T: McKenzie exercises up to 9 times, 1 mo R1: chiropractic manipulation up to 9 times R2: educational booklet	No significant differences in global improvement or functional status between T and R1, or T and R2.	
Chok et al., 1999 (34)	T = 30 R = 24	21–54	F, M	Subacute LBP	T: trunk muscle endurance exercises, up to 5 series of 10 reps for 6 cycles, 30–45 min, 3×/wk, 6 wk at physiotherapy department R: hot pack, advice, booklet	At 3 wk, reduced pain and improved function in T vs C, no differences at 6 wk.	
Coxhead et al., 1981 (40)	T = 150 R = 142	42	F, M	Acute and chronic LBP	T: range-of-motion exercises, first week daily, next 3 wk decreasing frequency R: traction or manipulation or corset, 4 wk	Comparable number of patients improved after 4 wk and 4 mo and in comparable degree on pain scale in both groups.	
Davies et al., 1979 (43)	T1 = 14 T2 = 14 R = 15	15–45	F, M	LBP between 3 wk and 6 mo duration	T1: extension exercises and diathermy, 4 wk T2: isometric flexion, strengthening trunk and abdominal muscles, diathermy, 4 wk R: diathermy, 4 wk	No significant difference between the groups in the number of patients showing improvement after 2 and 4 wk.	
Delitto et al., 1993 (47)	T1 = 14 T2 = 10	14–50	F, M	Acute or subacute LBP	T1: McKenzie extension and mobilization, supervised, 3×/wk, advice to train at home T2: Williams flexion exercises, supervised 3×/wk, advice to train at home	Functional status improved significantly more in T1 than T2 after 3 and 5 days.	
Deyo et al., 1990 (49)	T1 = 34 T2 = 29 R1 = 31 R2 = 31	18–70	F, M	Chronic LBP	T1: relaxation and stretching exercises (12), 2–3×/d, and TENS T2: exercises as above, and sham TENS R1: TENS (transcutaneous nervous stimulation) R2: sham TENS	More improvement of pain in T1+T2 than in R1+R2 after 4 wk. No significant differences in pain intensity or in functional status after 4 and 12 wk between the groups.	
Elnaggar et al., 1991 (56)	T1 = 28 T2 = 28 R = 98	20–50	F, M	Chronic LBP	T1: McKenzie extension exercises, 6 exercises, 10 repetitions, 30 min·d^{-1}, 7×/wk, 2 wk T2: Williams flexion exercises, 6 types, 10 reps, 30 min·d^{-1}, 7×/wk, 2 wk R: usual primary care management	No significant difference between the groups regarding decrease of pain.	
Faas et al., 1993 (60)	T = 156 R2 = 162 R1 = 155	16–65	F, M	Acute LBP	T: stretching, flexion, isometric abdominal exercises, individually by physiotherapist, 20 min, 2×/wk, 5 wk R1: usual care R2: placebo ultrasound	No significant differences between the groups in change of pain, recurrences of pain, or functional status except NHP energy more improved in T than in R1 during first 3 mo.	
Farrell and Twomey, 1982 (62)	T = 24 R = 24	20–65	F, M	Acute LBP	T: isometric flexion exercises for abdominal muscles and diathermy, 3×/wk, 3 wk, advice to exercise 3–4×/d at home R: passive manipulation	R significantly more effective than T regarding the number of symptom-free patients within 2 wk. No difference in pain score after 3 wk between the groups.	
Frost et al., 1995, 1998 (68,69)	T = 36 R = 35	18–55	F, M	Chronic LBP	T: fitness program, 8 1-h sessions during 4 wk and back school R: back school, advice on exercise	Functional status and pain improved significantly more after 4 wk in T than R. After 6 mo functional status more improved in T than R. After 2 yr reduction in functional status significantly less in T than R.	
Hansen et al., 1993 (82)	T = 60 R1 = 59 R2 = 61	21–64	F, M	(Sub)chronic LBP	T: intensive dynamic back muscle training, 5 series, 10 reps, total 300 contractions, 1 h, 2×/wk, 4 wk R1: physical therapy including slowly progressive back and abdominal muscle exercise, 1 h, 2×/wk, 4 wk R2: placebo	No significant differences in pain level between groups after treatment and after 1, 6, and 12 mo. Overall treatment effect was significantly better in T and R1 than in R2 at all evaluations.	
Hemmilä et al., 1997 (95)	T = 35 R1 = 45 R2 = 34	17–64	F, M	Chronic LBP	T: a variety of bending and rotation exercises 10×/d, stretching maximum 10×/h, 6 wk R1: gentle mobilization, maximum 10×/h, 6 wk R2: various, largely passive physiotherapy modalities, 10×/h, 6 wk	R1 had improved more than T at 6 mo, no other differences between groups in pain measures.	

TABLE 2. *Continued*

Reference	Subjects: N	Subjects: Age	Subjects: Sex	Subjects: Group	Exercise Training	Results	Comment
Johansen et al., 1995 (102)	T1 = 13 T2 = 14	18–65	F, M	Chronic LBP	T1: dynamic back, neck, and abdominal endurance exercises, stretching, maximum 100 reps, 1 h 2×/wk, supervised, 3 mo T2: coordination and balance exercises, 2×/wk, supervised, 3 mo	No significant differences between the groups in changes of pain or function.	
Kankaanpää et al., 1999 (105)	T = 30 R = 24	40 ± 8	F, M	Chronic LBP	T: supervised progressive exercises for trunk muscle function and coordination with specific equipment 24 sessions, 1.5 h, 12 wk, instructions for home exercise R: passive treatments considered to have placebo effect	Back pain intensity and functional disability decreased and lumbar endurance improved significantly more in T than in R at 1-yr follow-up.	
Kendall and Jenkins, 1968 (115)	T1 = 14 T2 = 14 T3 = 14	Not reported	Not reported	Chronic LBP	T1: isometric strengthening exercises for abdominal and trunk muscles, 12 reps, 3×/d, postural advice T2: mobilization and strengthening exercises, 6 types, 6–12 reps, 2×/d, postural advice T3: strengthening extension exercises for back extensors, 5 types, 6–12 reps, 2×/d, postural advice	Significantly more improved patients in T1 than in T2 after 1 and 3 mo.	
Klaber Moffett et al., 1999 (120)	T = 89	18–60	F, M	LBP between 6 wk–6 mo duration	T: supervised strengthening, stretching and relaxation exercises, 8 sessions, 1 h, 4 wk, brief back education	During 1-yr follow-up, T compared with R showed significantly greater improvement in disability score and back pain scale, reported less days off work (378 vs 607), and used fewer health care resources.	
Lidström and Zachrison, 1970 (144)	T1 = 21 R = 21 T2 = 20	21–61	F, M	Chronic LBP	T1: strengthening exercises for back and abdominal muscles, mobilizing exercises, 10 treatments by physiotherapist, 1 mo T2: isometric strengthening of abdominal and hip extensor muscles, 6 times each, pelvic traction, 10 treatments by physiotherapist, 1 mo R: hot packs, rest	T2 patients improved significantly more in 4 wk and needed less analgesics after treatment than T1 and R patients.	
Lindström et al., 1992 (145) and 1992 (146)	T = 51 R = 52	41 ± 11	F, M	Chronic LBP	T: back school, ergonomics, individual submaximal strength and endurance training by various exercise modes, 3×/wk until return to work R: usual care	Significantly more T patients than R patients returned to work in 6 and 12 wk, and duration of absence from work significantly shorter in T than R during the 2nd follow-up year. No intergroup difference in functional status after 1 yr.	
Ljunggren et al., 1997 (149)	T = 64 R = 62	18–65	F, M	Chronic LBP	T: physiotherapy exercises, back muscle strengthening, stretching, 3 series, 10 reps, 3×/wk, 12 mo R: specific exercises with "TerapiMaster," strengthening exercises for back, thigh, buttocks, abdominal and chest muscles, 12 mo	No differences between groups in days of absence from work at 12 mo and 24 mo. No differences between groups in days of absence from work at 12 mo and 24 mo.	
Malmivaara et al., 1995 (156)	T = 52 R1 = 67 R2 = 67	41	F, M	Acute LBP	T: back extension and lateral bending exercises at home until pain subsided, individual instructions from physiotherapist R1: bed rest and advice to continue ordinary activities as tolerated R2: advice to avoid bed rest and to continue ordinary activities as tolerated	Significantly better outcome on functional status at 3 wk in R2 than in T.	
Manniche et al., 1988 (158)	T1 = 27 T3 = 31 T2 = 32	20–70	F, M	Chronic or recurrent LBP	T1: intensive supervised back extensor strengthening exercise 2 times 50 reps each exercise, 30 sessions, 1.5 h, 3 mo T2: mild isometric exercises, 10 reps, 8 sessions, 1 h, 1 mo, massage T3: mild back extensor strengthening exercises, identical to T1 but 20 reps each exercise in 45 min	Significantly more improvement in T1 than in T2 and T3 in physical impairment index after 3 and 9 mo.	
Manniche et al., 1993 (159)	T1 = 31 T2 = 31	18–74	F, M	Chronic LBP	T1: intensive dynamic exercises plus hyperextension, 2 sessions, 1–1.5 $h \cdot wk^{-1}$, 24 sessions in 3 mo T2: intensive dynamic exercises as in T1 but no hyperextension	Overall improvement not significantly different between the groups, but significantly more improvement of pain in T1 than in T2 at 3 mo.	
Mannion et al., 1999 (160)	T1 = 49 T2 = 50 T3 = 49	45 ± 10	F, M	Chronic LBP	T1: individually prescribed active physiotherapy including exercises, 2×/wk, instructions for home training, 3 mo T2: progressive strengthening of trunk muscles by specific equipment, 2×/wk, 1 h, 3 mo T3: progressive low-impact, aerobic exercises and stretching, in classes, 2×/wk, 3 mo	All three treatments were equally efficacious in reducing pain intensity, pain frequency, and disability in daily tasks immediately after treatment. These effects were well maintained over the following 6 mo with the exception of disability regressing toward pretreatment value in the physiotherapy group.	
Martin et al., 1980 (164)	T1 = 12 T2 = 12 R = 12	20–58	F, M	Chronic LBP	T1: supervised strengthening and mobilizing abdominal and back muscle exercises, 20 min, 3×/wk, 3 wk, advice to exercise at home T2: supervised isometric exercises to strengthen abdominal and pelvic floor exercises, 20 min, 3×/wk, 3 wk, advice to train at home R: detuned ultrasound and diathermy, 20 min, 3×/wk, 3 wk	T1 and R improved significantly more on pain intensity at 5 weeks than T2.	

TABLE 2. *Continued*

Reference	Subjects: *N*	Age	Sex	Group	Exercise Training	Results	Comment
Nwuga, 1982 (185)	T = 25 R = 26	20–40	F	Acute LBP	T: isometric flexion exercises of back and abdominal muscles, 10 contractions, 3×/wk until no pain, diathermy, education R: spinal manipulation, 3×/wk until no pain, education	Spinal flexion and SLR improved significantly more in R than T. No data given on pain, global improvement, or functional status.	
Nwuga and Nwuga, 1985 (186)	T1 = 31 T2 = 31	20–40	F	Acute LBP	T1: McKenzie extension exercises prescribed by physiotherapist T2: Williams flexion exercises prescribed by physiotherapist	Significantly more improvement of pain in T1 than in T2.	
O'Sullivan et al., 1997 (189)	T = 22 R = 22	16–49	F, M	Chronic LBP	T: training of deep abdominal muscles at home, 10–15 min·d^{-1}, 10 wk R: usual care including various exercises	Significantly more improvement of pain and functional status in T than in R after treatment and up to 30 mo.	
Risch et al., 1993 (206)	T = 31 R = 23	22–70	F, M	Chronic LBP	T: dynamic extension exercises 2×/wk, 4 wk, then 1×/wk, 6 wk R: waiting list controls	Pain score and physical disability score improved significantly more in T than in R from before to after treatment.	
Sachs et al., 1994 (214)	T = 14 R = 16	35 ± 8	F, M	Chronic LBP	T: work tolerance rehabilitation: stretching, strengthening, and cardiovascular training, 4–6 h plus strength training on B-200 Isostation R: work tolerance rehabilitation only	No significant difference in range of motion after 3 wk.	
Seferlis et al., 1998 (220)	T = 60 R1 = 60 R2 = 60	19–64	F, M	Acute LBP	T: intensive strength, endurance, and coordination training in groups, 3×/wk, 8 wk	No significant intergroup differences in pain or functional status at 1, 3, and 12 mo or in the number of days off work because of back pain after 1 yr.	
Snook et al., 1998 (226)	T = 43 R = 42	30–60	F, M	Chronic or recurrent LBP	T: 45-min video instruction for a variety of exercises, training at home R: advice to avoid lumbar flexion for the first 2 h of every day	Baseline differences between groups. No direct comparison of effects between groups, but R improved more.	
Stankovic and Johnell, 1990, 1995 (231,232)	T = 50 R = 50	34 ± 10	F, M	Acute LBP	T: McKenzie extension exercises R: mini-back school	Significantly less pain and better spinal mobility in T than in R after 3 wk and 1 yr.	
Torstensen et al., 1998 (240)	T1 = 71 T2 = 70 R = 67	20–65	F, M	Chronic LBP	T1: mobilizing and stabilizing exercises in groups, total about 1000 reps/session, 3×/wk, 12 wk T2: self-organized walking, 1 h, 3×/wk, 12 wk R: conventional physiotherapy, 1 h, 3×/wk, 12 wk	Significantly greater decrease of low back pain in T1 and R than in T2 after 1 yr, and in leg pain in T1 and R than in T2 after treatment. Significantly better functional status in T1 and R than in T2 after treatment and after 1 yr.	
Turner et al., 1990 (242)	T1 = 24 T2 = 24 R1 = 25 R2 = 23	20–65	F, M	Chronic LBP	T1: aerobic exercises, 20 min, 5×/wk, 60–70% HRmax, 8 wk T2: identical to T1 plus behavioral therapy, spouses participated, 8 sessions·wk^{-1}, 2 h R1: behavioral program identical to T2; no aerobic training R2: waiting list control	T2 improved significantly more than T1 and R2 after treatment. No significant intergroup differences after 6 and 12 mo.	
Underwood and Morgan, 1998 (244)	T = 35 R = 40	16–70	F, M	Acute LBP	T: teaching of McKenzie principles, other advice, home exercises R: usual care, general advice	No significant intergroup differences in functional status and pain intensity after 4, 12, and 52 weeks, but back pain was reported to be no problem after 1 yr in 50% of T and 14% in R.	
Waterworth and Hunter, 1985 (261)	T = 34 R1 = 36 R2 = 38	18–50	F, M	Acute LBP	T: flexion and extension exercise plus passive physiotherapy 5×/wk, 10–12 d R1: NSAIDs, 10 d R2: spinal manipulation and mechanical therapy according to McKenzie, 5×/wk, 10–12 d	No significant differences between groups in pain, mobility, or overall improvement.	
White, 1996a (263)	T1 = 76 T2 = 72		M	Chronic LBP, received workmen's compensation	T1: mild static trunk exercises, back exercise classes, calisthenics in pool, physiotherapy until improvement or deterioration T2: vigorous flexion and extension exercises, heavy occupational therapy until improvement or deterioration	No significant difference between the groups in the number of patients showing improvement.	
White, 1996b (263)	T = 99 R = 95	19–60	M	Chronic LBP, received workmen's compensation for the condition	T: hospital bed rest, progressive activities until heavy, 6 wk unless fit for work earlier R: usual care	During 3 mo after discharge from study higher percentage of T patients (42%) than R patients (15%) showed satisfactory result at work.	
Zylbergold and Piper, 1981 (269)	T1 = 10 T2 = 10 R = 8	25–65		Patients from waiting list for physiotherapy	T1: instruction to perform pelvic tilt flexion exercises at home, 2×/wk, 1 mo T2: instructions for back care and pelvic tilt exercises at home R: manual therapy, 2×/wk, 1 mo	No intergroup differences in pain, functional status, or mobility after 1 mo.	

T, training; R, reference group; F, female; M, males.

effects may be mainly because of other than physiological conditioning effects of training. If so, then the type and dose of exercise could not be logically determined using physiological training principles, but effective activity would depend mainly on individual preferences and perceptions, and circumstantial factors. On the other hand, musculoskeletal and cardiorespiratory deconditioning effects as a consequence of cLBP follow known biological principles, and strong evidence (Category A) shows that those kinds of effects can be diminished or abolished by appropriate PA. It is likely that the known dose-response relationships of PA would apply in those kinds of programs. Return to work is not a recommendable outcome measure in studying the effects of physical activity on LBP patients, because return to work depends strongly on many factors unrelated to the effects of PA.

Recommendations for research. Given the great public health significance of LBP and the evidence of effectiveness of PA (as one of few promising modalities) in its primary and secondary prevention, this area of research should be given high priority. Development of and wide international agreement on standardized methodology to assess and rate LBP is required in order to improve the quality and comparability of studies on this field.

Incomplete knowledge of the causes and mechanisms of the symptoms in the LBP syndrome hampers advancement of research targeted at their prevention and alleviation. Thorough research on this area is needed.

The possible preventive and provoking roles of various types and intensities of PA in the occurrence of LBP should be searched by large-scale, long-term, prospective population studies using close monitoring of PA and other living habits, injuries, and symptoms as well as assessments of health-related fitness.

Given the evidence of effectiveness of exercise regimens in secondary prevention of cLBP, sufficiently large-scale, carefully planned, conducted, and documented clinical, preferably RCTs, should be conducted comparing different exercises alone or as parts of a common basic program. A clear distinction in the aims and design of the studies should be made whether the measures are targeted to influence the primary features of the syndrome or the deconditioning effects resulting from prolonged inactivity or hypoactivity.

OA

Background. OA is a chronic degenerative joint disease characterized primarily by progressive loss of articular cartilage. Loss of cartilage leads to narrowing of the joint space. The clinical syndrome of OA is diagnosed when, in addition to the radiological findings, narrowing of joint space, and osteophytes, the patient presents also symptoms and signs such as joint pain, restriction of motion, crepitus with motion, joint effusions, and deformity (24).

Articular cartilage is highly resistant to stress caused by physical loading. However, sudden single or repetitive impact or torsional loadings can damage articular cartilage and the calcified subchondral bone region. Acute disruption of normal articular cartilage requires contact stresses between the adjacent surfaces of 25 MPa (megapascals, newtons per square meter) or more. The peak articular contact stresses in, for example, running, jumping, and throwing are in the range of 4–9 MPa. These kinds of activities are unlikely to cause damage in healthy joints as evidenced by extensive animal experiments (24,94). However, chronic or repetitive stresses less than 25 MPa may cause articular surface damage or degeneration. Several studies show strong association between chronic or repetitive increased mechanical loading especially in occupational work and development of OA (190). Slowly applied loads allow the cartilage to deform and muscle contraction to absorb much of the energy and stabilize the joint. Therefore, the joints tolerate slowly applied loads much better than sudden impacts or torsional loading. Aging leads to alterations that may increase the probability of cartilage degeneration and OA (24).

The above considerations suggest that in searching for dose-response relationships between PA and development of OA, the focus in dose should be primarily on the size of impact loadings on the joints, the rate of the force application, the number of repetitions of high-impact loading, and the total time during which these loadings occur. One dimension of the dose is also the degree of torsion of the movement causing the loading. In ambulatory persons, the forces on joint surfaces caused by locomotion cannot be measured. Ground reaction forces of, for example, walking, running, and jumping can be measured, but the forces transmitted to the joint surfaces vary greatly, depending especially on the damping caused by muscles and their contraction at the time of the impact (24). Thus, dose-response relations of PA and development of OA in human studies have to be examined in descriptive, in best case semiquantitative terms.

Animal studies have shown that moderate PA causes beneficial structural and functional alterations in joints (94,213). However, it has not been shown that PA could prevent development of OA in ambulatory subjects through the physiological benefits. Indirectly, high PA may have a preventive effect by counteracting development of obesity, a strong risk factor for OA. Evidence from RCTs indicates that patients with OA can benefit from PA as a secondary preventive measure. Thus, examination of dose-response relationships between PA and OA is indicated also in the context of secondary prevention.

Review of research evidence. The following review is limited to examination of the role and dose-response relationships of PA and development and secondary prevention of OA to OA of hip and knee joints because these are the most relevant conditions in terms of the scope of this review.

PA and development of OA. Several studies on workers in different occupations have found increased prevalence of OA in loaded joints (190,253). Corresponding observations have been made on athletes in a number of sport disciplines (24,74,128,190,218). Because of a number of factors it is not possible to accurately define dose-response

relationships between loading and OA in sports. These factors include differences in individual susceptibility to OA; strong self-selection to begin; and continuation/discontinuation of a certain sport because of such issues as differences in experiencing musculoskeletal symptoms, differences in exercise patterns, and differences in the number of subclinical and overt injuries. However, by combining the findings of incidence and prevalence studies and the current understanding of the harmful effects of impact and torsional loading on joints, it is possible to group sports and other activities into risk categories on the basis of estimated differences in intensity; frequency; and rate of joint injury, impact, and torsional loading (24). In this classification, recreational aerobic activities (especially in water) belong in the low loading category, and most ball games as well as competitive running in the high loading sports. The role of injury in the genesis of OA is strongly substantiated by several previous (210,218) and by a newly published 36-yr follow-up study on 1321 former medical students who gave information of living habits, injuries, and health in annually repeated self-administered surveys. In those reporting injury on the corresponding joint at entry to the cohort or during the follow-up, the risk of developing OA of the knee was 5.17-fold and that of hip OA 3.5-fold that of those not reporting injury (70).

Several studies indicate that among the participants of the same sport, OA of knee or hip is more common in elite compared with recreational athletes (88). The risk of OA has been found to increase with the exposure time (hours per week and duration of activity in years) to sport and recreational PA (230,254) (only in a group of active controls, N = 138,216,255) (Table 3). Occupational loading added to sport loading increases the risk of OA in the loaded joint (216,254,255). Running offers the most favorable opportunities for examination of dose-response relationships between sport and risk of OA, although self-selection causes difficulties in the interpretation of the findings. Eight of the 14 studies reviewed by Panush and Inzinna (190) and Gross and Marti (74) did not find significant differences in OA risk between runners and various control groups. In two of the included studies (168,175) the higher frequency of OA in knee or hip in runners was ascribed to anatomic abnormalities. In a 9-yr follow-up of previously reported runners (135,136) showing no difference in OA between runners and controls, Lane et al. (137) did not find significant differences in knee or hip OA or their progression between runners and controls (Table 4).

Moderate levels of PA have not been found to be associated with increased risk of OA in several population-based studies (31,64,81,99,138,166,216,254,255), but the risk was significantly increased in the most active subjects in several of these studies (31,64,81,99,138,166,216,254,255). Three of these studies (64,81,166) are follow-up investigations of the same cohort (Table 5). The dose associated with significantly increased risk of OA expressed in easily understandable terms was at least 4 $h \cdot d^{-1}$ of heavy PA for radiographic and at least 3 $h \cdot d^{-1}$ for symptomatic OA of the knee in one study (166) and running at least 20 $miles \cdot wk^{-1}$ for hip or knee OA in another study (31).

In conclusion, no studies have shown evidence for direct preventive effects of PA against development of OA of the weight-bearing joints in ambulatory subjects. Light and moderate activities even in large amounts have not been shown to increase the risk (Category C), but several epidemiological studies of various designs in general and selected populations show evidence (Category C) that a large amount of heavy PA for a long period of time increases the risk of OA of the loaded joints. Limited information suggests that the amount of heavy PA associated with increased risk is several hours a day for many years, probably decades. Sports that cause a large amount of high impacts and torsional loading of joints involve especially high relative risk. These observations agree well with the results from RCTs in animals. Dose-response relationships between PA and OA are obscured by several intervening factors, e.g., differences in individual susceptibility, performance technique, and equipment used.

PA and secondary prevention of OA. A recent systematic review of RCTs on this topic (248) summarizes most of the current evidence (until September 1997). Thirteen publications on 11 trials were assessed for effectiveness of exercise therapy in patients with OA of the hip or knee (Table 6). Six trials satisfied at least 50% of the validity criteria. Effect sizes indicated small to moderate beneficial effects of exercise therapy on pain. Small beneficial effects were found on self-reported and observed disability and walking, and moderate to great beneficial effects on patients' global assessment of effect. Thus, the reviewed studies show modest beneficial short-term effects of exercise therapy in patients with OA of the knee and to a lesser extent in patients with hip OA (only one trial). Hardly any information is available on long-term effects of exercise therapy. Results of the four trials comparing effects of different exercise programs remained inconclusive.

Two additional randomized trials are worth reviewing. One study found that low-intensity cycling (40% of heart rate reserve (HRR)) for 10 wk was as effective as high-intensity cycling (70% of HRR) in improving function and gait, decreasing pain, and increasing aerobic capacity in older subjects (157). Cycling did not increase acute pain in either group. Deyle et al. (48,187) evaluated the effectiveness of a program combining manual therapy and range-of-motion, strengthening, stretching, and aerobic (stationary bicycle and walking) exercises for 4 wk on 83 patients with knee OA randomized in active and placebo treatment groups. At 1 yr, the treated patients showed clinically and statistically significant gains over baseline scores on knee function, pain and stiffness, as well as on walking distance. Twenty percent of the patients in the placebo group and 5% of the patients in the treatment group had undergone knee arthroplasty. Pertinent information of these two studies is included in Table 6.

In conclusion, there is evidence that PA, especially in the form of supervised exercises, is effective in the treatment and rehabilitation of patients with knee OA (Category B).

TABLE 3. Association of OA and level or exposure time of PA in sports and recreational activities.[a]

Author	Type of Study	Population	Osteoarthritis	Physical Activity	Association	Comment
Roos et al., 1994 (210)	Case-control	71 elite and 71 nonelite ex-soccer players, 142 age-matched controls, age $\bar{x}$ 61–63 yr.	Radiographically confirmed knee OA	Soccer playing	Prevalence of OA: 15.5% in ex-elite, 4.2% in ex-nonelite players, and 2.8% in controls. Exclusion of subjects with knee injuries: higher rate among ex-elite players but no difference between ex-nonelite players and controls.	The increased prevalence of knee OA in ex-elite soccer players without diagnosed knee injuries suggests that the sport itself at this level may result in OA.
Sandmark and Vingård, 1999 (216)	Case-referent	Study population: all men born between 1921 and 1938 and living in 14 counties during the period 1991–1995. Cases: subjects who had knee prosthetic surgery because of primary OA in 1991–1993, 325 men and 300 women. Referents: randomly selected from the study population, 264 men and 284 women. Subjects with trauma, surgery or disease affecting the knee region were excluded.	Primary OA of the knee requiring prosthetic surgery	The same procedures as in the two studies above	Relative risk of developing severe knee OA was 2.9 [1.3–6.5] in men aged 55–65 yr who were highly exposed to all kinds of sports. Cross-country skiing, soccer, ice hockey and bandy, and track and field increased the risk in men but jogging did not. Occupational loading added to the risk attributable to sports. No associations were found in women.	Moderate daily generally was not associated with risk of knee OA.
Spector et al., 1996 (230)	Retrospective cohort study	81 female ex-athletes, 40–65 yr, and 977 age-matched female controls invited to clinical and radiological examination.	Radiographically confirmed hip or knee OA	Detailed information of current and past participation in sports and other physical activities by nurse- or self-administered questionnaire	Age, height, and weight adjusted OR for OA of patella-femoral joint was 2.97 [1.15–7.67] and OR for OA of hip was 1.60 [0.73–3.48] in ex-athletes. Within the control group, a subgroup reporting long-term vigorous exercise had risks of OA similar to those of ex-athletes.	No clear risk factors were seen in the ex-athletes.
Vingård et al., 1993 (254)	Case-control	Study population: all 50 to 70-yr-old men in the referral area of four hospitals. Cases: men who received a total hip replacement because of primary OA during 4 yr, N = 247. Controls: randomly from the population, N = 322. Subjects with history of injury excluded.	Primary OA of hip requiring prosthetic surgery	Detailed information of participation in various sports by interview, each exposure (in hours) was aggregated to the age of 49 and also in two periods: to 29 and 30–49 yr of age	Risk of developing hip OA increased with medium exposure (total number of hours) (RR, 1.3–2.6) and high exposure (RR, 2.8–4.5) but not with years of low exposure. Medium and high occupational loading added to the risk because of sport loading (both high; RR, 8.5 [4.0–17.9]).	Most hazardous sports seemed to be track and field sports (RR, 3.7) and racket sports (RR, 3.3).
Vingård et al., 1998 (255)	Case-control	Study population: all 50 to 70-yr-old women in five counties. Cases: women who had received total hip replacement because of primary OA during 4 yr, N = 230. Controls: randomly from the population, age-matched, N = 273.	Primary OA of hip requiring prosthetic surgery	As in the study above, but aggregation of exposure to age 50	Relative risk of developing hip OA was 2.3 [1.5–3.7] for those with high and 1.5 [0.9–2.5] for those with medium sport exposure. Medium and high occupational load added to the risk because of sport loading (both high; RR, 4.3 [1.7–11.0]).	Physical load from sporting activities seems to be a moderate risk factor for women for development of severe OA of the hip.

RR, relative risk; OR, odds ratio.
[a] 95% confidence intervals are given in brackets. $\bar{x}$ denotes mean.

Only limited evidence is available regarding hip OA. The evidence comparing effectiveness of different exercise regimens is inconclusive. Dose-response relationships have been reported in only one RCT and it suggests that low-intensity stationary bicycling is as effective as higher intensity stationary biking (Category B).

Recommendations for research. Intensive PA, particularly sports that include rapid movements, high impacts,

TABLE 4. Studies of running and risk of developing OA of the hips or knees.[a]

Reference	Subjects	Mean Age (yr)	Training		Site	Diagnostic Method	Risk and Comments
			Yr	Amount			
Puranen et al., 1975 (201)	74 champion runners	56	21		Hip	Clinical, radiographic	No more hip OA than in nonrunners
McDermott and Freyne, 1983 (168)	20	35	13	48 miles·wk^{-1}	Knee	Radiographic, clinical	High incidence (30%) of knee OA, attributed to previous injuries and anatomic abnormalities
Sohn and Micheli, 1985 (229)	504 ex-runners	57	9–15	18–29 miles·wk^{-1}	Hip, knee	Clinical	No association between moderate long distance running and development of OA
Lane et al., 1986 (133)	41 distance runners	58	9	4.5 h·wk^{-1}	Hip, knee	Radiographic, clinical	No difference to controls in clinical OA among male or female runners
Panush et al., 1986 (191)	17 ex–long-distance runners	53	12	28 miles·wk^{-1}	Hip, knee	Radiographic	Comparable low prevalence of OA in runners and matched controls
Lane et al., 1987 (134)	498 distance runners	59	12	27 miles·wk^{-1}	Hip, knee	Clinical	No difference to controls in conditions thought to predispose to OA
Marti et al., 1989 (163)	27 ex–long-distance runners	42	20	50–100 km·wk^{-1}	Hip	Clinical, radiographic	Incidence of moderate to severe OA 16% in runners, 0% in controls; best predictors of OA: age, distance run, speed
Konradsen et al., 1990 (124)	27 ex–long-distance runners	58	40	20–40 km·wk^{-1}	Hip, knee	Clinical, radiographic	No significant differences in the signs of OA between runners and matched controls
Kujala et al., 1994 (128)	199 ex–elite long-distance runners	50 at entry	Not given	Not given	Hip, knee, ankle	Hospital admissions because of OA	Age-adjusted OR for hospitalization 1.84 (0.93–3.61) in ex-runners compared to controls; mean age at first admission 70.3 yr, in controls 61.2 yr
Kujala et al., 1995 (129)	28 ex-runners	60	30	Total 9500 h	Knee		Risk of developing OA in runners not increased (RR, 1.06)
Lane et al., 1995 (132)	35 nonelite long-distance runners	65	10–13	3 h·wk^{-1}	Hip, knee	Clinical, radiographic	Same incidence of OA in runners and matched controls
Lane et al., 1998 (137)	28 nonelite long-distance runners	66	17	2 h, 18 miles·wk^{-1}	Hip, knee	Clinical, radiographic	Radiographic hip OA and progression of radiographic knee OA similar for runners and matched controls

[a] See also Spector et al. 1996 (230); Sandmark and Vingård, 1999 (216) in Table 3; and Cheng et al., 2000 (31), in Table 5.

torsional loads, and injuries on joints are shown to increase substantially the risk of development of OA. An important task for research is to develop measures to decrease the size of impacts and torsional loadings on joints in PA, especially in running and ball games, as well as to develop measures to decrease the risk of joint injuries.

Short-term effectiveness of PA in secondary prevention of knee OA is shown. Long-term effectiveness of PA should be tested and comparison of effectiveness of different regimens is needed. Especially important is comparison of low-intensity and higher intensity activities on various aspects of OA. These aspects should be studied also in patients with OA of the hip.

OP

Background. OP is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. These changes can be assessed indirectly through noninvasive measurement of areal bone mineral density (BMD), measured in grams per square centimeter. Bone density accounts for 75–85% of the variance in ultimate strength of bone tissue. Low bone mass by itself causes few, if any, symptoms except in severe OP. Thus, OP is defined most commonly by an intermediate outcome (BMD), not by a health outcome (e.g., fracture) (177).

BMD is considered normal if it is no lower than 1 SD below the mean for young adult women. BMD between 1.0 and 2.5 SD below the mean indicates osteopenia or low bone mass and BMD 2.5 SD or more below the young adult means indicates osteoporosis (268). Fracture risk increases 1.5- to 3-fold for each SD fall in BMD (162). Age-adjusted risk of hip fracture is increased 2.4- to 3-fold for each 1 SD decline in BMD (42). One SD is around 10% of BMD. Prevention of OP can be defined as preventing BMD from dropping lower than 2.5 SD below the mean for young adult women. Two factors determine the amount of bone later in

TABLE 5. Association of OA and PA in various populations.[a]

Author	Type of Study	Population	Osteoarthritis	Physical Activity	Association	Comment
Imeokparia et al., 1994 (99)	Case-control	Cases: 85 men, 154 women Controls: randomly from the same community sample, 85 men, 154 women. Age in all groups: mean 66–67 yr	Knee radiographically confirmed	Retrospectively by interview, occupational, leisure-sport, home-based, four levels in each by estimated energy expenditure, collapsed to high and low	In high PA women age-adjusted OR 1.66 [1.0–2.72], persisted when controlled for confounders. No significant association in men. History of knee injury did not alter the risk estimations.	In women, risk increased slightly with increased BMI.
Lane et al., 1999 (138)	Cross-sectional	5818 women over 65 yr, age $\bar{x}$ 72 yr, recruited from populations of four areas	Hip, radiographically confirmed and symptomatic	Detailed recreational PA retrospectively by questionnaire	For women in the highest quartile of PA (1–5×/wk vs lowest quartile) OR significantly increased [1.4–1.7 depending on age at the time of exposure]. Corresponding findings regarding symptomatic OA.	Moderate participation in recreational PA was associated with OA of hip.
Framingham Study						
Hannan et al., 1993 (81)	Longitudinal cohort study	1404 subjects (584 men, 820 women), mean age 73 yr	Knee, radiographically confirmed	Amount and intensity questioned by interview at examinations 29 and 12 yr prior to the diagnostic procedures	No significant association between habitual PA and OA of knee in men or women.	Habitual physical activity was not found to be a risk factor for knee OA.
Felson et al., 1997 (64)	Longitudinal cohort study, follow-up time 9 yr	598 subjects without knee OA at baseline, mean age 70.5 yr, 63.7% women; part of the cohort of the previous study	Knee, radiographically confirmed 8–9 yr after the baseline examination	Amount and intensity questioned by interview at examinations 29 and 12 yr prior to the baseline assessment and at 4 yr during the follow-up	OR for OA increased significantly with increasing habitual PA being 3.3 [1.4–7.5] in the highest quartile. Risk increased in subjects both with and without knee symptoms at baseline or during follow-up.	High BMI at baseline and increase of weight during follow-up increased the risk of knee OA especially in women.
McAlindon et al., 1999 (166)	Longitudinal cohort study	470 subjects (177 men, 293 women) without knee OA at baseline, mean age 70.1 yr	Knee, radiographically confirmed and symptom-based 8–9 yr after the baseline examination	Detailed inquiry of the type, amount, and intensity of PA about in the middle of the follow-up	Increasing amount of heavy PA was associated with increased risk, e.g., OR for ≥ 4 h·d^{-1} compared with no heavy PA = 7.0 [2.4–20]. No association with light or moderate PA and knee OA.	Increase of BMI increased the risk of knee OA.
Cheng et al., 2000 (31)	Prospective, mean follow-up 10 yr	16,961 subjects, 20–87 yr examined at Cooper Clinic	Physician-diagnosed knee or hip; OA reported by the subject in follow-up survey	Amount of walking/jogging or other regular PA at baseline as reported by the subject	Hazard ratio 2.4 [1.5–3.9] (controlled for other potential risk factors) in men under age 50 reporting high levels of PA (running 20 or more miles·wk^{-1}). No association among older men or women.	Increasing BMI increased the risk especially in women; moderate-intensity PA levels recommended by recent public health guidelines are not likely to increase risk of hip or knee OA.

[a] 95% confidence intervals are given in brackets. $\bar{x}$ denotes mean.

life: the bone mass accumulated during youth (peak bone mass) and the subsequent rate of bone loss.

PA can influence bone mass by causing compressive or bending loads on bone. These can cause a temporary deformation, strain, in bone leading to primary and secondary responses in bone that stimulate bone formation. These responses have been shown to be proportional to the load in cell and organ cultures and in animal models (225). The purpose of these responses can be thought of as parts of a homeostatic mechanism that aims to keep deformation of bone because or mechanical loading within narrow limits. High loads lead to increased bone formation and decreased bone loss and low loading leads to decreased bone formation and increased resorption (67). Findings from animal studies support the concept of bone as a "mechanostat" (243). Also, human studies ranging from the effects of immobilization and inactivity through sedentariness to active lifestyle, recreational exercise, and intensive sports practice show decrease, maintenance, and increase of BMD corresponding to this model. However, the stress-strain relationships regarding bone's adaptation are complex. Current knowledge derived especially from animal experiments suggests that bone's adaptation to loading is determined by three basic rules (243): 1) dynamic rather than static loading is effective; 2) only short duration of mechanical loading is necessary to initiate an adaptive response and the capacity of bone tissue to respond to the stimulus at one time is saturated by few loading cycles; and 3) bone cells accommodate to a customary loading, making them less responsive to routine loading signals.

Application of these basic rules to practical exercise regimens means that each session should include movements causing high loads at high rates, i.e., they should be forceful and fast, and they should load the bone from variable directions, but the number of movements need not be great. The loading can be caused by gravitational forces or by muscular contractions. The forces have to focus specifically on the targeted bone area in order to be

TABLE 6. RCTs on the effectiveness of exercise training in patients with OA of the hip or knee.

Reference	N	Subjects	Exercise Training			Results
			Mode and Intensity	Frequency	Duration	
Minor et al., 1989 (171)	80	64 yr, males and females, OA of hip, knee	T1: walking, 60–80% HRmax T2: aerobic aquatics, R: range of motion (control)	3×/wk	12 wk	The walking and aquatics exercise groups showed significant improvement over the control group in aerobic capacity, 50-foot walking time, depression, anxiety, and PA.
Kovar et al., 1992 (126)	102	70 yr, males and females, OA of knee	T: walking + patient education R: usual care (control)	3×/wk, 30 min	8 wk	Significant 18% improvements in walking distance, 39% improvement in functional status, 27% decrease in pain in the walking group, significantly different from the changes in the control group.
Börjeson et al., 1996 (19)	68	64 yr, OA of knee	T: exercises to increase strength and ROM R: no treatment	3×/wk, recommended to be done also at home	5 wk	Significant improvement of perceived knee status and of descending steps in T, not in R. Only small objective improvements in functions.
Schilke et al., 1996 (219)	29	65 yr, most females, OA of knee	T: muscle strengthening R: nonexercising control group	3×/wk, 6 sets of 5 maximum contractions	8 wk	Significant subjective improvements in pain, stiffness, mobility, and arthritis activity, more improvement in strength measures in the experimental as compared to the control group.
Bautch et al., 1997 (10)	30	69 yr, OA of knee	T: ROM exercises, individualized low-intensity walking, education R: education	3×/wk, 1 h 1×/wk, 1 h	12 wk 12 wk	Significant decrease in pain in T, no change in R.
Ettinger et al., 1997 (59)	439	70 yr, males and females, OA of knee	T1: walking, 50–70% HRR T2: calisthenics R: health education	3×/wk, 40 min	3 mo facility + 15 mo home	Modest but consistent improvements in self-reported pain and disability and better scores on performance measures of function compared with those participating in health education programs. Greater improvements in those completing more exercise.
van Baar et al., 1998 (247)	201	40–85 yr, males and females, OA of hip or knee	T: individualized exercises for muscle strength and length, mobility, coordination, movement abilities, and locomotion administered by physiotherapist	12 wk		Significantly larger decrease of pain (medium effect size) and observed disability (small effect size) in T than in R.
Mangione et al., 1999 (157)	39	71 yr, males and females, OA of knee	Stationary cycling T1: 70% HRR T2: 40% HRR	3×/wk, 25 min	10 wk	Both T1 and T2 improved significantly and similarly in several objectively measured functions and in the amount of overall pain. Cycling did not increase acute pain in either group.
O'Reilly et al., 1999 (187)	191	62 yr, males and females with knee pain	T: strengthening exercises R: no intervention	Daily at home	6 mo	Pain scores and physical function scores improved more in T than in R.
Deyle et al., 2000 (48)	83	60 (T), 62 (R) yr, males and females, OA of knee	T: manual therapy and supervised knee exercise program (stretching, ROM, and strengthening exercises) R: placebo	2×/wk and at home	4 wk	In T, significant improvement in walking performance and standardized OA assessment score over baseline at 4 and 8 wk and 1 yr, not in R. By 1 yr, patients in R had significantly more knee surgeries than patients in T.

T, training; R, reference group; ROM, range of motion.

effective. Loading has to repeat frequently and continuously in order to maintain BMD, and loading has to increase periodically if the aim is to stimulate continuing increase of bone mass.

Review of research evidence. Peak bone mass accumulated in youth and the subsequent rate of bone loss are thought to be equally important in determining bone mass at age 70. Numerous cross-sectional studies in athletes (258) (Tables 7–9) and in population samples (37,54,97,104,183, 239,245,246,262) (Table 10), some longitudinal studies (4,12,36,39,142,161,173,202) (Tables 11 and 12), and at least seven RCTs (17,20,66,77,172,227,265) (Table 13) and a

TABLE 7. Bone mineral mass in female athletes taking part in high-magnitude loading sports (results selected from cross-sectional studies).

Reference	Athlete Group	N	Age (yr)	Bone Site	Bone Mineral Mass: Difference Between Athletes and Controls (%)	Technique
Flodgren et al., 1999 (65)	Flatwater sprint kayakers	10 (6 M, 4 F) (6 M, 4 F)	19	Total body Head		DXA
	Matched controls	20	19	Ribs	6.4*	
				Humerus (L/R)	10.4*/11.7*	
				Legs L/R		
				Femur neck L/R		
				Femur Ward's L/R		
				Femur trochanter L/R		
				Spine	10.9*	
				Lumbar spine		
				Pelvis	5.1*	
				Arms (BMC) L/R	15.7*/10.6*	
Davee et al., 1990 (44)	Muscle-building	9	20–30	L2–L4	+10*	DPA
	Controls	9				
Heinonen et al., 1993 (87)	Weight-lifters	18	25 ± 5	L2–L4	+15*	DXA
				Femoral neck	+10*	
				Distal femur	+19*	
				Patella	+22*	
				Proximal tibia	+12*	
				Calcaneus	+4*	
				Distal radius	+29*	
	Controls	25	23 ± 3			
Heinrich et al., 1990 (92)	Body-builders	11	26 ± 5	L2–L4	+12*	DPA
				Femoral neck	+15*	
				Ward's triangle	+23*	
				Greater trochanter	+12*	
				Proximal radius	+9*	SPA
				Distal radius	+16*	
	Controls	18	25 ± 4			

M, males; F, females; L, left; R, right; DPA, dual photon absorptiometry; DXA, dual-energy x-ray absorptiometry; SPA, single photon absorptiometry.
* $P < 0.05$.

nonrandomized controlled trial (73) show evidence (Category A) that physical activity in youth can contribute to increased peak bone mass (33,52,140,257). The cited studies do not allow quantitative dose-response analysis, although their findings generally agree with the results of animal experiments regarding the characteristics of effective loading stimulus described above and allow categorization of physical activities according to their characteristics and potential to influence bone mass (258). Thus, weight-bearing activities producing high-magnitude (Table 7) and high-rate (impact) (Table 9) loadings stimulate effectively bone formation, and non–weight-bearing activities without these characteristics such as swimming even in large amounts has not been shown in any study to increase BMD at any site in female subjects (3,29,38,51,57,63, 141,188,236,238).

Unfortunately, it is not known whether and in what degree and by what kind of physical activity the increased peak bone mass attained by exercise training can be preserved for decades until old age. Limited information suggests that much or most of it may be lost during adult years (107–109), but diminution of peak bone mass can be deterred by substantially less PA than what was practiced while gaining it (6,91,118,125).

Clinically relevant studies to analyze possible dose-response relationships between PA and prevention of OP are RCTs and other controlled trials in middle-aged and elderly women with bone mass (density) as the primary outcome. Most of these studies have been analyzed in several recent thorough reviews (14,58,111,112,113,140,212,260,266). The newest analyses by Wolff et al. (266) and Wallace and Cumming (260) cover the non-RCTs to the end of 1996 and RCTs to the beginning of 1998. Pertinent information of most randomized and nonrandomized exercise training trials on bone mass in pre- and postmenopausal women is summarized in Table 14. The reviews agree well on quantitative results and on most views and can be summarized as follows. Quantitative analyses show strong evidence (Category A) that PA can be effective in maintaining bone mass in premenopausal and decreasing substantially loss of bone in postmenopausal women. This effect was 1) about $1\%\cdot yr^{-1}$ in favor of the exercising subjects, 2) mainly because of decreased rate of loss of bone in the exercisers, 3) seen both in lumbar spine and femoral neck, and 4) seen in both pre- and postmenopausal women. Both endurance or aerobic and strength or progressive resistance training as well as impact and nonimpact exercises can be effective, and no definite differences between the types of training were seen. However, only a few studies were available to analyze the effect of nonimpact exercise or strength training on the hip in premenopausal women. The results of studies using high-intensity strength training were more consistent and showed positive effects compared with those using low-intensity resistance training (140). The size of the effect of exercise training on bone mass was found to be comparable to that of calcium supplementation.

The reviews pointed out several shortcomings of the studies such as heterogeneity of subjects, training programs, and measurements; small sample sizes; and short duration and inadequate description and quantification of the training programs. In general, the training program characteristics,

TABLE 8. Bone mineral mass in female athletes taking part in repetitive loading (weight bearing) sports (results selected from cross-sectional studies).

Reference	Athlete Group	*N*	Age (yr)	Bone Site	Bone Mineral Mass: Difference Between Athletes and Controls (%)	Technique
Dook et al., 1997 (51)	Running and field hockey	20	46 ± 3	Whole body	+7*	DXA
				Regional leg	+7*	
				Regional arm	+3	
	Sedentary controls	20	46 ± 2			
Harber et al., 1991 (83)	Eumenorrheic runners	17	27 ± 5	Calcaneus	−2	CST
	Amenorrheic runners	11	26 ± 6	Calcaneus	0	
	Normoactive controls	14	27 ± 7			
Heinonen et al., 1993 (87)	Orienteers	30	23 ± 3	L2–L4	0	DXA
				Femoral neck	+2	
				Distal femur	+5*	
				Patella	+3*	
				Proximal tibia	+4*	
				Calcaneus	+4	
				Distal radius	+1	
	Cross-country skiers	28	21 ± 3	L2–L4	0	
				Femoral neck	+5	
				Distal femur	+5	
				Patella	+2	
				Proximal tibia	+3	
				Calcaneus	+3	
				Distal radius	−1	
	Active controls	25	23 ± 3			
Heinonen et al., 1995 (88)	Orienteers	30	23 ± 3	L2–L4	+8	DXA
				Femoral neck	+3	
				Distal femur	+6*	
				Patella	+4	
				Proximal tibia	+7*	
				Calcaneus	+11	
				Distal radius	−4	
	Speed skaters	14	21 ± 9	L2–L4	+6	
				Femoral neck	+4	
				Distal femur	+7*	
				Patella	+5	
				Proximal tibia	+6	
				Calcaneus	+3	
				Distal radius	−6	
	Cross-country skiers	28	21 ± 3	L2–L4	+3	
				Femoral neck	+5	
				Distal femur	+5	
				Patella	+2	
				Proximal tibia	+5*	
				Calcaneus	+9*	
				Distal radius	−7*	
Kirk et al., 1989 (119)	Long-distance runners	10	25–35	T12–L3	+1	QCT
	Sedentary controls	10				
	Long-distance runners	9	55–65	T12–L3	−7	
	Sedentary controls	9		Midradius	+1	
Lane et al., 1986 (133)	Long-distance runners	6	56	L1	+35*	QCT
	Matched controls	6	56			
Myerson et al., 1992 (176)	Eumenorrheic runners	13	30 ± 1	Total body	+10*	DPA
	Amenorrheic runners	13	30 ± 1	Total body	−7	
	Controls	12	27 ± 1			
Petterson et al., 2000 (194)	Cross-country skiers	16	16 ± 0.3	Total body	+1.8	DXA
	Normoactive controls	16	16 ± 0.7	Head	+0.9	
				Humerus right	+6.9*	
				Humerus left	+9.2*	
				Humerus diaphysis right	+5.1	
				Humerus diaphysis left	+8.1*	
				Spine	−0.9	
				Femoral neck	+8.9*	
				Femoral diaphysis	+7.6*	
				Distal femur	+5.0	
				Greater trochanter	+9.3*	
				Proximal tibia	+6.6	
				Tibia diaphysis	+2.1	
Suominen et al., 1992 (235)	Long-distance runners, skiers	18	66 –85	Calcaneus	+12 and +6	SPA
	Population sample	42	70–81			
Wolman et al., 1991 (267)	Runners	21	25–28	Femoral shaft	+8*	DPA
	Rowers	36	24–26	Femoral shaft	+2	
	Sedentary controls	13	27–30			

CST, Compton scattering technique; DPA, dual photon absorptiometry; DXA, dual-energy x-ray absorptiometry; QCT, quantitative computed tomography; SPA, single photon absorptiometry.
* $P < 0.05$.

TABLE 9. Bone mineral mass in female athletes taking part in sports producing strains on bones at a high rate (e.g., impacts) and usually from many directions (results selected from cross-sectional studies).

Reference	Athlete Group	*N*	Age (yr)	Bone Site	Bone Mineral Mass: Difference Between Athletes and Controls (%)	Technique
Alfredson et al., 1997 (1)	Volleyball	13	21 ± 4	Whole body	+6.1*	DXA
				Head	−1.8	
	Matched normoactive controls	13	25 ± 2	Lumbar spine	+13.2*	
				Femoral neck	+15.8*	
				Ward's triangle	+17.9*	
				Trochanter	+18.8*	
				Whole femur dominant/nondominant	+5.8/+8.2*	
				Humerus dominant/nondominant	+9.5*/10.0*	
Courteix et al., 1998 (38)	Gymnasts	18	10 ± 1	Whole body	+14.4*	DXA
				Midradius	+15.5*	
	Controls	13	11 ± 1	Distal radius	+33	
				L2–L4	+11*	
				Femoral neck	+15*	
				Trochanter	+11	
				Ward's triangle	+15*	
Dook et al., 1997 (51)	Basketball and netball	20	46 ± 3	Whole body	+8*	DXA
				Regional leg	+8*	
				Regional arm	+4	
	Sedentary controls	20	46 ± 2			
Düppe et al., 1996 (53)	Active football players	96	18 ± 4	Total body	+4*	DXA
				Lumbar spine	+5	
				Femoral neck	+11*	
				Trochanter	+11*	
				Ward's triangle	+11*	
	Controls	90	20 ± 5			
	Former football players	25	40 ± 5	Total body	+4*	
				Lumbar spine	−2	
				Femoral neck	+7*	
				Trochanter	+11*	
				Ward's triangle	+9*	
	Controls	57	37 ± 4			
Fehling et al., 1995 (63)	Volleyball players	8	20 ± 1	L2–L4	+11*	
				Femoral neck	+15*	
				Ward's triangle	+17*	
				Total body	+13*	
				Left arm	+5*	
				Right arm	+7*	
				Left leg	+15*	
				Right leg	+12*	
				Right pelvis	+19*	
	Gymnasts	7	20 ± 1	L2–L4	+14*	
				Femoral neck	+15*	
				Ward's triangle	+17*	
				Total body	+11*	
				Left arm	+15*	
				Right arm	+16*	
				Left leg	+10*	
				Right leg	+10*	
				Right pelvis	+15*	
	Controls	13	20 ± 1			
Haapasalo et al., 1994 (79)	Squash players	19	18–32	Proximal humerus	+9*	DXA
				Humeral shaft	+10*	
				Radial shaft	+1*	
				Ulnar shaft	−1*	
				Distal radius	+10*	
				Distal ulna	+24*	
				Calcaneus	+12*	
	Controls	19	19–33			
Heinonen et al., 1995 (88)	Squash players	18	25 ± 4	L2–L4	+14*	DXA
				Femoral neck	+17*	
				Distal femur	+11*	
				Patella	+7*	
				Proximal tibia	+13*	
				Calcaneus	+19*	
				Distal radius	+11*	
	Aerobic dancers	27	28 ± 4	L2–L4	+3	
				Femoral neck	+9*	
				Distal femur	+3	
				Patella	+2	
				Proximal tibia	+6*	
				Calcaneus	+14*	
				Distal radius	−8*	
	Controls	25	24 ± 5			

TABLE 9. *Continued*

Reference	Athlete Group	*N*	Age (yr)	Bone Site	Bone Mineral Mass: Difference Between Athletes and Controls (%)	Technique
Jacobson et al., 1984 (101)	Tennis players	11	18–22	Spine	+11*	DPA
				Distal radius	+17*	SPA
				Midradius	+12*	
				Metatarsal	+23*	
	Age-matched controls	11				
Kannus et al., 1995 (106)	Tennis and squash players	105	16–50	Proximal humerus	+10*	DXA
				Humeral shaft	+10*	
				Radial shaft	+3	
				Distal radius	+8*	
				Calcaneus	+11*	
	Controls	50	16–48			
Kirchner et al., 1995 (117)	Gymnasts	26	20 ± 0.2	Lumbar spine	+18*	DXA
				Total proximal femur	+21*	
				Femoral neck		
				Ward's triangle		
				Whole body	+22*	
					+25*	
					+10*	
	Controls	26	20 ± 0.2			
Kirchner et al., 1996 (118)	Former gymnasts	18	36 ± 1	Lumbar spine	+16*	DXA
				Femoral neck	+18*	
				Ward's triangle	+22*	
				Whole body	+9*	
	Controls	15	37 ± 1			
Lee et al., 1995 (141)	Volleyball players	11	19 ± 1	Total body	+17	DXA
				Lumbar spine	+18	
				Femoral neck	+11	
				Trochanter	+17	
				Ward's triangle	+4	
				Spine	+6*	
				Pelvis	+10*	
				Left arm	+12*	
				Right arm	+13*	
				Left leg	+17*	
				Right leg	+15*	
	Basketball players	7	20 ± 2	Total body	+9*	
				Lumbar spine	+14*	
				Femoral neck	+20*	
				Trochanter	+24*	
				Ward's triangle	+18*	
				Spine	+5*	
				Pelvis	+11*	
				Left arm	+12*	
				Right arm	+17*	
				Left leg	+15*	
				Right leg	+17*	
	Soccer players	9	19 ± 1	Total body	+4	
				Lumbar spine	+6*	
				Femoral neck	+10*	
				Trochanter	+16*	
				Ward's triangle	+12	
				Spine	+5	
				Pelvis	+7*	
				Left arm	+1	
				Right arm	+3	
				Left leg	+11*	
				Right leg	+11*	
	Sedentary controls	11	22 ± 1			
Nichols et al., 1994 (180)	Gymnasts	11	19 ± 1	Preseason:		DXA
				Lumbar spine	+8*	
				Femoral neck	+11*	
	Controls	11	21 ± 2			
Nichols et al., 1995 (181)	Basketball players	14	19 ± 1	L2–L4	+10*	DXA
				Femoral neck	+14*	
				Total body	+10*	
				Leg	+15*	
				Arm	+8*	
	Gymnasts	15	19 ± 1	L2–L4	+9*	
				Femoral neck	+11*	
				Total body	+5*	
				Leg	+7*	
				Arm	+12*	

TABLE 9. *Continued*

Reference	Athlete Group	*N*	Age (yr)	Bone Site	Bone Mineral Mass: Difference Between Athletes and Controls (%)	Technique
	Tennis players	6	23 ± 4	L2–L4	+4*	
				Femoral neck	+3*	
				Total body	+6*	
				Leg	+9*	
				Arm	+6*	
	Volleyball players	13	19 ± 1	L2–L4	+13*	
				Femoral neck	+14*	
				Total body	+10*	
				Leg	+15*	
				Arm	+8*	
	Nonathletes	12	21 ± 2			
Nichols-Richardson et al., 2000 (182)	Gymnasts	16	10 ± 2	Whole body		DXA
				Femur		
	Matched controls	16	10 ± 1	L1–L4		
Pearce et al., 1996 (192)	Ballet dancers: <40 mo oligomenorrhea	17	14 ± 0.2	Lumbar spine	−2	DXA
				Femoral neck	+9*	
				Ward's triangle	+10*	
				Trochanter	+9*	
				Arms	−4	
	>40 mo oligomenorrhea	24	18 ± 0.2	Lumbar spine	−4	
				Femoral neck	+4	
				Ward's triangle	+4	
				Trochanter	+2	
				Arms	−8	
	Controls	46	18 ± 0.2			
Pettersson et al., 2000 (195)	Rope-skipping	10	18 ± 1	Whole body	+7*	DXA
				Humerus, right	+10*	
	Normoactive controls	25	18 ± 1	Lumbar spine	+14*	
				Femoral neck	+10*	
				Trochanter	+14*	
				Total femur	+4*	
				Femur diaphysis	+8*	
				Tibia diaphysis	+20*	
				Radius UD	+33*	
				Radius proximal	6	
Rissner et al., 1990 (207)	Volleyball players	12	20 ± 2	Lumbar spine	+15*	DPA
				Calcaneus	+26*	SPA
	Basketball players	9	20 ± 1	Lumbar spine	+12*	
				Calcaneus	+36*	
	Nonathletes	13	20 ± 2			
Robinson et al., 1995 (208)	Gymnasts	21	22 ± 3	Whole body	+2	DXA
				Lumbar spine	+6	
				Femoral neck	+12*	
	Controls	19	19 ± 2			
Sandström et al., 2000 (217)	Ice hockey	14	22 ± 4	Whole body	+7*	DXA
				Head	−3	
	Normoactive controls	14	22 ± 4	Lumbar spine	+9*	
				Femoral neck	+18*	
				Ward's triangle	+20*	
				Trochanter	+22*	
Slemenda and Johnston, 1993 (223)	Figure skaters	22	10 – 23	Total body	+7*	DXA
				Spine	+6	
				Trunk	+8*	
				Legs	+10*	
				Pelvis	+14*	
				Arm	+4	
	Controls	22	10 – 23			
Söderman et al., 2000 (228)	Soccer	41	16 ± 0.3	Whole body	+3*	DXA
				Head	−2	
	Normoactive matched controls	41	16 ± 1	L2–L4	+6*	
				Femoral neck, dominant	+10*	
				Ward's triangle	+10*	
				Trochanter	+17*	
Taaffe et al., 1995 (236)	Gymnasts	13	19 ± 1	Whole body	+3	DXA
				Lumbar spine	+8	
				Femoral neck	+15*	
				Trochanter	+15*	
	Controls	19	19 ± 2			
Taaffe et al., 1997 (237)	Gymnasts, 8-mo cohort	26	20 ± 1	Whole body	+1	DXA

TABLE 9. *Continued*

Reference	Athlete Group	*N*	Age (yr)	Bone Site	Bone Mineral Mass: Difference Between Athletes and Controls (%)	Technique
				Lumbar spine	+6	
				Femoral neck	+14	
	Controls	14	19 ± 2			
	Gymnasts, 12-mo cohort	8	19 ± 1	Whole body	+4	
				Lumbar spine	+4	
				Femoral neck	+20*	
	Controls	11	20 ± 2			

DPA, dual photon absorptiometry; DXA, dual-energy x-ray absorptiometry; SPA, single photon absorptiometry.
* $P < 0.05$.

such as its duration and the background characteristics of the subjects (i.e., hormone replacement, smoking, or use of alcohol), did not influence the results substantially in the primary and subgroup analyses. However, low compliance was considered to explain poor results in some studies. The design of the study seemed to influence the results substantially, because in the review of Wolff et al. (266), the effect of training was almost twice as high in non-RCTs compared with RCTs.

Since the completion of the above-cited reviews, new RCTs (8,46,80,90,91,155,197,215), randomized trials without a control group (98,123), and nonrandomized, controlled studies (100,264) on middle-aged and older women and men have been published. The aims, subjects, exercise programs, and measurements are also heterogeneous in these studies. Regarding dose-response issues, the studies in general support the notion that high-intensity exercise can increase or maintain bone mass in premenopausal women (8,90,264) and elderly men (155), but that high-intensity resistance training was not effective in postmenopausal women not on hormone replacement therapy (166), and the same high-impact exercise program that was effective in premenopausal was not effective in postmenopausal women (8). Heinonen et al. (90) found that a multiexercise intensive (about 70% $\dot{V}O_{2max}$) endurance program consisting of walking, stair climbing, ergometer cycling, and jogging for 18 months in perimenopausal women resulted in maintenance of prestudy femoral neck BMD, and the trend of change was significantly different from that in the control group. A calisthenics (dynamic strength-endurance exercises for trunk, pelvis, hip, and lower limbs) program was not effective regarding maintenance of bone mass at the trained sites. The proposed explanation for the findings is that the strength-endurance exercises did but the calisthenics exercise did not fulfil the conditions for effective osteogenic stimulus in terms of the magnitude, rate, and distribution of the stress applied on bones. An extension study of an RCT showing positive effect of high-impact exercise on femoral neck BMD in premenopausal women supports the idea that the results on bone can be maintained with less-demanding training than that used in the original program (91).

Humphries et al. (98) did not find changes in lumbar spine BMD in older women taking or not taking hormone replacement therapy in a high-intensity strength training program despite substantial increase in muscle strength, but the duration of the program was only 24 wk. Kohrt et al. (123) compared supervised high-intensity resistance endurance and physiotherapy program for 9 mo in elderly women and men with physical frailty and found significant increase or trend of increase on hip and spine BMD in the high-intensity group and decreasing trend in the home exercise group in changes of whole body and Ward's triangle BMD. The differences between the group changes were statistically significant. None of the studies cited above showed a moderate- to low-intensity exercise program to influence bone mass in pre- or postmenopausal women, in frail elderly persons (46), or in patients with rheumatoid arthritis (80), except for one study. Iwamaoto et al. (100) found that, in postmenopausal osteoporotic women on calcium and vitamin D_3 supplementation, daily outdoor walking (documented by step counters) and gymnastics for 12 mo increased lumbar spine BMD significantly in relation to a nonexercising control group.

PA is related not only to increased but also to decreased bone mass, particularly in women. A large volume of intensive training for prolonged periods such as seen especially in competitive runners can lead to osteopenia. The mediating mechanisms are complicated and not completely known, but one mechanism is disruption of normal ovarian function that leads to inhibition of the production of gonadotropin-releasing hormone by the hypothalamus and to decreased estrogen content in blood. These athletes have oligorrhea or amenorrhea and gradually bone mass decreases, or in young athletes peak bone mass remains low. As a consequence, the risk of stress fractures increases, but it is not definitively known if the risk of osteoporosis in later life is also increased (11,71). In addition to hormonal disturbances, low body mass and, frequently, eating disorders can contribute to athletes' osteopenia. No quantitative dose-response relationship regarding this condition has been defined.

Concluding remarks. The available information from published studies does not allow definition of any quantitative dose-response relationships between PA and bone mass, a surrogate indicator of OP. Basic bone research indicates the existence of dose-response relationships but also that they are complicated because of the fact that several factors in the dose, especially the magnitude, rate, and directions of the loads, determine the response and these relationships change with the adaptation of the bone to a

TABLE 10. Studies on association of bone mass and PA in various population samples.

Reference	Type of Study	Population	*N*	Age (yr)	PA	Bone Site, Method	Findings	Comments
Cooper et al., 1995 (37)	Cross-sectional (for PA)	Women born in a city during 2 yr	153	21	Several indices of past and current PA by interview	Lumbar spine, femoral neck, DXA	Dose-related association between lumbar (5% difference between least and most active, $P = 0.07$) and femoral neck (12% difference $P < 0.01$) BMD and amount (min·d^{-1}) of outdoor leisure walking.	PA was the strongest lifestyle determinant of BMD.
Düppe et al., 1997 (54)	Cross-sectional	Random sample of the 15 to 42-yr-old population of a city	395	15–42	Current leisure time, occupational, and transport PA by validated questionnaire	Spine, proximal femur, DXA	No association between BMD and PA in 15 to 16-yr-old subjects, but in 21 to 42-yr-old men significantly (9%) higher femoral BMD in highly active (vs least active) subjects. In women similar but nonsignificant trend.	Occupational activity showed similar but weaker association to femoral BMD.
Ho et al., 1997 (97)	Cross-sectional	Invited sample of women clients of a medical clinic	273	21–40	Minnesota Leisure Time PA questionnaire, previous 12 mo, activity in METs	L2–L4 proximal femur, DXA	In highly active 21 to 30-yr-old women, spine and femur BMD significantly (6–7%) higher than in less active women. No influence of PA on BMD in the older women was seen.	
Jones and Dwyer, 1998 (103)	Cross-sectional	A cohort of 8-yr-old children	330, 115 girls, 215 boys	8	Sports participation and other PA by questionnaire, aerobic capacity and strength measurements	Lumbar spine, femoral neck, total body, DXA	In boys, sports participation was associated with 4% higher hip and spine BMD. In girls, PWC_{170} was associated positively with hip and spine BMD.	
Kanders et al., 1988 (104)	Cross-sectional	Convenience sample	60 women	25–34	Minnesota Leisure Time PA questionnaire	Lumbar spine (DXA), radius (SPA)	No relation between radius BMD and PA. Vertebral BMD correlated significantly to energy expenditure of PA, r = 0.41. About 8% difference in vertebral BMD among less and more active women (cut point, 970 kcal·d^{-1} in PA)	Additive effect of Ca and PA.
Nordström et al., 1997 (183)	Cross-sectional	A convenience sample of men with low or moderate level of PA	33	25	Detailed history of participation in exercise and sports by interview	Total body, L2–L4, femoral neck, Ward's triangle, trochanter, humerus and head, DXA	The amount of PA (hours per week) at the time of peak bone mass attainment was significant predictor of BMD of the total body and the sites at proximal femur in these young men with low to moderate level of PA.	
Ruiz et al., 1995 (211)	Cross-sectional	A convenience sample of young girls and boys	151	7–15	Detailed data of participation in sports and exercise by interview	L1–L4, femoral head and neck, trochanter, upper third of femoral diaphysis	Weekly duration of sports activity significantly influenced vertebral and femoral sites, especially in girls and during puberty.	
Teegarden et al., 1996 (239)	Cross-sectional	Minimally active young women	204	18–31	Detailed self-reported data of PA during leisure and in occupation 5 yr before enrollment as well as sport participation in high school and college	Total body, femoral neck and spine by DXA, and radius by SPA	PA at high school or during 5 previous yr (expressed as estimated energy expenditure) were significant predictors of BMD or BMC at most measured sites.	
Valdimarsson et al., 1999 (245)	Cross-sectional	Random sample of women from one city	254	16, 18, and 20	Detailed data of sport and exercise participation during the last 3 mo by standardized questionnaire	Total body, lumbar spine, hip, and distal forearm	Especially weight-bearing activity correlated significantly with BMC and BMD of the measured sites in uni- and multivariate analyses. Positive relationship between training hours per week and total body BMD in all age groups; most marked from 0 to 3 h·wk^{-1} and among the 16-yr-olds. Thus, training >7 h·wk^{-1} associated with 4–6% greater BMD vs training <0.5 h·wk^{-1}.	

DXA, dual-energy x-ray absorptiometry; SPA, single photon absorptiometry.

TABLE 11. Longitudinal observational studies with repeated PA assessment and bone measurements only at the end of the follow-up period.

Reference	Type of Study	Population	*N*	Age (yr)	PA	Bone Site, Method	Findings
Kemper et al., 2000 (114)	Longitudinal cohort study, longitudinal data of PA	A cohort of school children formed in 1977	182, males and females	28	Metabolic and mechanic PA during the last 3 mo by interview, neuromotor and cardiorespiratory fitness. All variables also from previous assessments since age 13.	Lumbar, femoral neck, and radius BMD by DXA at the end of follow-up period	Both PA indicators and neuromotor (but not cardiorespiratory) fitness significantly positively related to lumbar and femoral but not to radius BMD.
Lloyd et al., 2000 (150)	Longitudinal cohort study, longitudinal data of PA	A cohort representing white adolescents attending public school in one region	81	18	Detailed sport and exercise participation between ages 12–18 by standardized questionnaire	Total body, proximal femur by DXA at the end of the follow-up period	Cumulative sport-exercise scores between ages 12 and 18 yr associated with hip BMD at age 18 yr ($r = 0.42$). The amount of PA that distinguishes a sedentary from active (nearly daily basis) teenager is related to significant (~5%) increase in peak hip BMD.
Välimäki et al., 1994 (246)	Prospective cohort study, longitudinal data of PA	Representative sample from five regions	264 (153 females, 111 males)	20–29	Summary score derived from question on weekly frequency of PA >30 min asked thrice in 12 yr prior to the bone measurement	L2–L4 and femoral neck by DXA at the end of the follow-up period	In most active quartile compared with least active after significant differences in BMD (adjusted for age and weight) were found: in men, 11% higher in femoral neck and 8% higher at lumbar spine; in women, 8% higher in femoral neck.

DXA, dual-energy x-ray absorptiometry.

given load. In accordance with these principles, there is strong evidence (Category A) that high-intensity loading in relation to the strength of the bone causes an osteogenic response specifically at the loaded bone site if the internal milieu is adequate. The evidence in also strong (Category A) showing that bone's responsiveness to external loading is highly dependent on the influence of female and male sex hormones. Evidence suggesting that low- to moderate-intensity exercise (in relation to the bone strength) causes an increased osteogenic response is weak (Category D). The characteristics of a minimum effective dose of an osteogenic stimulus are not known. Quantitative relationships regarding the rate of application of the force are not known, but static efforts and slow movements have been found to be ineffective or less effective than fast application of force (Category B). Some evidence suggests that a borderline between noneffective and effective loading in aerobic activities is around 70% $\dot{V}O_{2max}$, corresponding to fast or brisk walking or walking at or above anaerobic threshold (Category C). High-impact activities are likely to be effective (Category A). Data are not sufficient to make firm conclusions regarding the required number of loadings in one session or the interval between sessions. However, findings of studies on animals indicate a need for rather few loadings per session and rather frequent loadings, several times per week. Also, the duration of an exercise program necessary to achieve the full effect is not known, but duration of program did not influence the results of some meta-analyses. On the basis of bone biology, it is likely, however, that loading should be continued more than a half year so that its effects on BMD could be seen. Decreased loading leads to decrease of bone mass, but the dose-response relations between change of loading and change of bone mass are not known.

Recommendations for research. Elucidation of dose-response relationships between PA and bone mass requires development of detailed descriptions of the PA exposure in epidemiological studies and quantitative measures of the exercise regimens in clinical trials. Animal experiments provide a firm basis to test the effectiveness of PA on bone mass, and in agreement with the animal studies, high-impact and high-intensity activities have been shown to be effective in clinical trials. A major task for research is to develop methods to apply effective loading on the targeted (finally clinically relevant) areas. This requires innovative ideas and rational application of basic bone biological and biomechanical principles and techniques. An important research task is to increase understanding of the muscle-bone interaction and to manipulate it in such a way that the damping effect of muscles could be decreased in controlled ways, thus allowing the loading to influence the bone more directly and more effectively and more safely.

Additional adequately designed and conducted RCTs, especially on subjects with increased risk of OP, should be conducted to compare the effectiveness of different exercise regimens (doses) on BMD and other parameters related to bone strength.

Long-term (several years) RCTs should be conducted to see continuation or discontinuation of the effectiveness on bone mass of appropriate (progressive and nonprogressive) exercise regimens.

In contrast to other modalities influencing BMD (drugs, calcium), the effects of PA on bone are specific to the loaded sites. These effects on bone geometry, mass distribution, internal architecture, etc., may not be seen as significant changes in BMD, but they might have substantial effect on the breaking strength of bone. These possibilities should be tested.

The amount and other characteristics of loading needed to preserve the increased bone mass and other effects on bone

TABLE 12. Longitudinal observational studies with repeated PA assessments and bone measurements.

Reference	Type of Study	Population	*N*	Age (yr)	PA	Bone Site, Method	Findings	Comments
Bailey et al., 1999 (4)	6-yr longitudinal cohort study	A sample of school children in one city	113 (60 boys, 53 girls)	8–14 at the beginning	Detailed data at least twice a year by questionnaire	Total body, L1–L4, femoral neck annually by DXA	One yr after peak BMC velocity the most active quartile of boys exhibited 9% and girls 16% higher total body BMC compared with the respective values in the least active quartiles. Corresponding differences at the femoral neck BMC were 7% and 11%.	First study to demonstrate that growing skeleton responds to everyday PA by increased bone mineral accrual.
Bennel et al., 1997 (12)	12-mo longitudinal cohort study	A cohort of elite and subelite athletes and nonathlete controls	166 (85 men, 81 women)	17–26	Detailed information of historical PA by 5-yr periods between ages 5 and 19 by questionnaire, and current PA by questionnaire at baseline and at the conclusion of the study	Total body, upper limb, L1–L4, proximal femur, tibia/fibula, and foot by DXA	Over the 12 mo both athletes and controls showed modest increases in total body BMC and femur BMD ($P < 0.001$). Changes in bone density were independent of exercise status except at lumbar spine, were power athletes gained significantly more bone density than the other groups.	The findings provide further support for the concept that bone response to mechanical loading depends on the bone site and mode of exercise.
Cohen et al., 1995 (36)	7-mo longitudinal study	A group of novice rowers and age-matched controls	25 men	19	Detailed data of training and other PA by interviews and logs	L1–L4, femoral neck, trochanter, Ward's triangle by DXA	In rowers, BMD of L1–L4 increased by 3% ($P < 0.001$) and mean BMC by 4% ($P < 0.001$), no significant change in controls. No significant changes of BMD or BMC at femoral sites.	
Courteix et al., 1999 (39)	12-mo longitudinal study	A group of gymnasts and nonexercising children, swimmers as controls	35 women	12	Detailed data of training and other PA by interviews and logs	Whole body, L2–L4, femoral neck, intertrochanteric region, Ward's triangle, nondominant radius	Percentage changes in BMD before compared with after investigation tended to be greater in gymnasts.	
Leichter et al., 1989 (142)	14-wk longitudinal study	A sample of army recruits	223 men	18–21	Highly intensive military training at least 8 $h \cdot d^{-1}$, 6 $d \cdot wk^{-1}$	Absolute bone density (all mass constituents of bone per unit volume) of distal tibia by Compton scattering technique	Mean bone density in the right and left distal tibia increased significantly by 8%.	Because of the strenuousness of the training 45% of the subjects experienced stress fractures.
Margulies et al., 1986 (161)	14-wk longitudinal study	A sample of army recruits	268 men	18–21	Highly intensive military training at least 8 $h \cdot d^{-1}$, 6 $d \cdot wk^{-1}$	BMC of distal tibia by single-beam photon absorptiometry	Mean BMC of the left distal tibia increased by 11% and that of right tibia by 5%.	Participation in the very hard training was interrupted in 41% of the subjects, mainly because of stress fractures.
Morris et al., 1999 (173)	18-mo longitudinal study	A group of rowers and matched controls	24 women	14–15	Top-level school based rowing training in rowers, no formalized exercise outside school in controls	Total body, proximal femur, femoral neck, L2–L4 by DXA	L2–L4 bone accrual of ovulatory rowers significantly greater (BMC 8%, BMD 6%) than that of the anovulatory rowers (BMC 1%, BMD 4%) and ovulatory controls (BMC 0.5%, BMD 1%). No differences in total body or femoral bone measurements among groups.	Osteogenic benefits of rowing were less when training was associated with low estrogen and progesterone metabolite excretion.
Recker et al., 1992 (202)	Longitudinal prospective study of up to 5 yr, average 3.4 yr	A sample of students from two universities	156 women	Average 21 at entry	By accelerometer (Caltrac) for 4 d prior to each 6-mo visit	L2–L4 and forearm every 6 mo, total body twice (early in study and at last visit)	Significant bone gain at each site in these women in their third decade. The rate of spinal bone gain correlated positively with the amount of PA. Estimated effect of activity ranges from 0.3% to 8.4% between least and most active women, none of the subjects exercising heavily.	

DXA, dual-energy x-ray absorptiometry.

TABLE 13. Nonrandomized (NRCT) and RCT exercise training trials studying the effect of PA on bone mass.

Reference	Type of Study	Population	*N*	Age (yr)	PA	Bone Site, Method	Findings	Comments
Blimkie et al., 1996 (17)	6-mo RCT	A group of postmenarcheal female students in one school, randomized to exercise and control group	36 females	14–18	Resistance exercises with machines, 3×/wk Controls: usual activity	Total body, lumbar spine by DXA	No significant differences in bone measurements between exercise and control groups.	
Bradney et al., 1998 (20)	8-mo RCT (randomized schools)	A group of prepubertal male students	40 boys	8–11	Variety of weight-bearing activities Controls: regular physical education classes	Total body, lumbar spine, pelvis, leg, head, arm by DXA	Significant intervention effect in total body and lumbar spine but not in hip.	
Friedlander et al., 1995 (66)	2-yr RCT	A group of recruited healthy women randomized to exercise training and stretching control group	127 women, 63 complete the study	20–35	Supervised aerobics and weight training, stretching for controls, Ca supplementation to both groups, 3×/wk, 1 h	Lumbar spine, femoral neck, and trochanter by DXA, L1–L3 by QCT, calcaneus by SPA	Significant positive differences in BMD between exercise and stretching groups for spinal trabecular, femoral neck and trochanteric, and calcaneal measurements, and exercise group demonstrated significant gain in BMD for spinal integral (1.3%), femoral trochanteric (2.6%), and calcaneal (5.6%) measurements.	Combined aerobics and weight training has beneficial effects on BMD in young women.
Gleeson et al., 1990 (73)	12-mo NRCT, training group and matched control group	Recruited premenopausal eumenorrheic sedentary to very active subjects	68 women	Average 33 ± 6	Upper and lower extremity weight training, with machines, 3×/wk, 30 min, 60% 1 RM	Calcaneus by SPA, lumbar spine by DXA, three times	No significant changes in calcaneus. Lumbar BMD increased 0.8% (NS) in the training and decreased by 0.5% (NS) in the control group, but between matched pairs the difference was significant.	The intensity of the program was moderate and the exercises did not directly load the vertebrae.
Gutin et al., 1999 (77)	8-mo randomized, modified crossover study (PA–no PA or no PA–PA)	A group of obese children	79 obese boys and girls	7–11	Exercises with machines and games, 5×/wk, 40 min	Total body	Significant intervention effect in total body BMD.	
Morris et al., 1997 (172)	10-mo NRCT	Students of two schools assigned to training and students of two matched schools assigned to control subjects	71 premenarcheal girls	9–10	A variety of vigorous, high-impact aerobic exercises 3×/wk, 30 min per session for 10 mo	L2–L4, proximal femur, femoral neck by DXA in the beginning and at the end of the study period	The exercise group showed significantly greater gain of BMD compared with the controls: total body, 3.5% vs 1.2%; L2–L4, 4.8% vs 1.2%; proximal femur, 4.5% vs 1.3%; and femoral neck, 12.0% vs 1.7%.	High-impact, strength-building exercise was effective for bone mineral acquisition.
Snow-Harter et al., 1992 (227)	8-mo RCT	A group of recruited women students, randomly assigned to running, weight training, or control group	52 women, 31 complete the study	20	Running: HR 70–80%, HRmax, progressive, from 4 to 10 miles·wk^{-1}, 3×/wk Weight training: supervised, circuit training, 3×/wk, progressive intensity from 25–70% to 85% of the 1-RM at the time. Controls: maintenance of recreational activity	L2–L4, proximal femur by DXA	L2–L4 increased similarly and significantly in runners (1.3%) and weight trainers (1.2%) and significantly more than in controls. No significant changes in the femoral bone measurements.	Progressive running and weight training increased lumbar spine bone mineral in young women.
Witzke and Snow, 2000 (265)	9-mo NRCT	A group of postmenarcheal girls recruited specially for the exercise group from two schools, controls from the same schools matched for age and menarche	56	13–15	Variety of progressive exercises increasing strength of and causing moderate to high impacts (plyometric jump training) on especially lower extremities, 3×/wk, 30–45 min	Whole body, L2–L4, femoral neck, trochanter, (3.1% vs 1.9%)	Plyometric training may increase bone mass during adolescent growth.	

DXA, dual-energy x-ray absorptiometry; QCT, quantitative computed tomography; SPA, single photon absorptiometry; 1-RM, one-repetition maximum; HR, heart rate.

TABLE 14. Pertinent data of non-RCTs and RCTs studying the effect of PA on bone mass in pre- and postmenopausal women.

Type of Regimen	Reference	Subjects		Exercise Regimen(s)	Bone Measurements Site and Method	Results	Comments
		N	Age (yr)				
Premenopausal (and perimenopausal) women							
Strength/resistance training regimens, NRCTs	Rockwell et al., 1990 (209)	T = 10 C = 7	36–40	9 mo, 8-station circuit, 2×/wk, 12 reps × 2 sets, 70% 1 RM	LS, FM by DXA	BMD decreased in LS in T, no change in C.	Differences between the groups at baseline.
	Vuori et al., 1994 (256)	T = 12 C = 12	21–22	12 mo, unilateral leg press, 4×/wk, 10 reps × 5 sets, 80% 1 RM	LS, FN, distal femur, patella, proximal tibia, calcaneus, ΣBMC by DXA	No significant training effects in BMD (except increase in patella) but positive trend.	
Strength/resistance training regimens, RCTs	Lohman et al., 1995 (151)	T = 22 C = 34	28–29	18 mo, 3×/wk, 8–12 reps × 3 sets, 12 exercises, 75–80% 1 RM	Total body, LS, FN, arm, leg by DXA	BMD increased in LS and FN as compared with C.	
Aerobic, endurance, or impact training regimens, RCTs (and RT without C)	Bassey et al., 1998 (8)	Tpre = 30 Cpre = 25 Tpost = 69 Cpost = 54	38 36 55 54	6 mo in premenopausal and 12 mo in postmenopausal women, 50 vertical jumps on 6 d·wk^{-1} of mean height 8.5 cm	LS, FN by DXA	BMD FN increased significantly (2.8%) in premenopausal T and significantly more than in premenopausal C. In postmenopausal T and C no difference.	Same regimen effective in pre- but not in postmenopausal women.
	Heinonen et al., 1998 (90)	Tend = 34 Tcalist = 36 C = 35	52–53	18 mo, endurance 2–3×/wk, 50 min, 55–75% $\dot{V}O_{2max}$ Calisthenics 2–6×/wk, 50 min, strength-endurance exercises Controls: light stretching 1×/wk	LS, FN, calcaneus, distal radius by DXA, repeated 6 times	Significant training effect (maintenance) in FN of Tend, no training effects in LS or by calisthenics.	The movement in calisthenics training may have been too slow and pliant to result in effective loading stimulus.
	Heinonen et al., 1996 (89)	Timp = 49 C = 49	35–45	18 mo, 3×/wk, 60 min, jumping, calisthenics, progressive, in class Controls: maintenance of previous activities	LS, FN, trochanter, distal femur, patella, proximal tibia, calcaneus, dominant radius by DXA	Significantly greater increase of BMD of FN in Timp (1.6%) than in C (0.6%), no intergroup differences between the changes of BMD at the non–weight-bearing bone sites.	
	Humphries et al., 2000 (98)	Tweight = 35 Twalk = 29	45–65	24 wk, Twalk 2×/wk, 50 min, walking Tweight 2×/wk, 50 min, dynamic concentric and eccentric contractions Increased gradually to 90% 1 RM, 2–4 reps	LS by DXA	No significant group differences in LS BMD.	Training period only 24 wk.

T, training group; C, control group; DXA, dual-energy x-ray absorptiometry; RM, repetition maximum; HR, heart rate; SPA, single photon absorptiometry; DPA, dual photon absorptiometry; QCT, quantitative computed tomography.

TABLE 14. *Continued*

Type of Regimen	Reference	Subjects: *N*	Subjects: Age (yr)	Exercise Regimen(s)	Bone Measurements Site and Method	Results	Comments
	Salamone et al., 1999 (215)	T = 115 C = 126	47	18 mo, moderate-intensity aerobic activities and lowering dietary fat intake to lose weight	LS and FN by DXA	Annualized rate of FN BMD loss was twofold higher ($P < 0.015$) in the T (lifestyle intervention) (0.8%) than in the C (weight stable) (0.4%) group.	Large increases in PA attenuated LS BMD loss, no effect on FN BMD loss.
	Snow-Harter et al., 1992 (227)	TW = 12 Taer = 10 C = 8	20	8 mo TW: weight training 3×/wk, 3 sets, 8–12 reps, 85% 1 RM, 14 exercises; Taer: 3×/wk, running 70–80% HRmax, mileage increased	LS, proximal femur by DXA	BMD, LS increased significantly in TW ($1.8\%\cdot yr^{-1}$) and Taer ($2.0\%\cdot yr^{-1}$) compared with C ($-1.2\%\cdot yr^{-1}$).	
Postmenopausal women							
Strength/resistance training regimens, NRCTs	Beverly et al., 1989 (15)	T = 69 C = no, nontrained arm as control	62	1½ mo, 6×/wk, 30 sec, (mostly) unilateral squeeze tennis ball, 3 times consecutively, morning and night	Wrist BMC by SPA	Significant 3.4% BMC gain in trained wrist, nonsignificant 1.9% increase in nontrained wrist, no intergroup comparison reported.	
	Braith et al., 1996 (21)	T = 8 C = 8	56–62	6 mo, 2×/wk, 1 set 10–15 reps, 15 RM, 8 exercises	Total body, LS, FN by DXA	Significant increases in total body, LS and FN in T, no change in C.	Heart transplant patients.
	Menkes et al., 1993 (170)	T = 9 C = 7	50–70, males	16 wk, 3×/wk, 1–2 sets, 15 reps, 5 RM, 13 exercises	Total body, LS, FN by DXA	Increased FN (+6.5%) in T vs C (–1.3%).	
	Pruitt et al., 1992 (199)	T = 17 C = 10	54–56	9 mo, 3×/wk, 1 set, 1 rep, 10 RM, 11 exercises	Radius and ulna by SPA, LS and FN by DPA	Increased BMD in LS in T, decreased in C.	
	Peterson et al., 1991 (193)	Taer = 17 Taer + strength = 18 C = 19	36–37	1 yr; aerobic dancing (class): 3×/wk, 50 min Strength training (home): 3×/wk, 2 sets, 8–12 reps, 6 exercises	Radius, ulna and humerus by SPA, LS, proximal femur by DPA	Nonsignificant increase in humerus and proximal femur BMD in Taer + strength and Taer vs C	
	Simkin et al., 1987 (221)	T = 14 C = 26	53–74	5 mo, 3×/wk, 15 min, 4 forearm exercises	Distal radius by Compton scattering and by SPA	Increased BMD (3.8%) in radius in T vs decreased (–1.9%) in C (by Compton scattering).	
Strength/resistance training regimens, RCTs	Chow et al., 1987 (35)	Taer = 17 Taer + strength = 16 C = 15	50–62	1 yr; aerobic training: 3×/wk, 40 min, 80% HRmax Strength training 3×/wk, 10 reps, 10 RM, upper and lower body	Trunk, thighs calcium bone index by neutron activation analysis	Increased calcium bone index in Taer and Taer + strength vs C. No difference between Taer and Taer + strength.	
	Heikkinen et al., 1997 (96)	T = 13 C = 13	53	36 mo, 1×/wk exercises in fitness center + advice to exercise 2 $h\cdot wk^{-1}$	LS, FN, Ward's triangle, trochanter	Increased BMD in Ward's triangle and trochanter in T, decrease in C, intergroup differences significant.	The given results refer to those in exercising and nonexercising placebo group of a drug trial.

TABLE 14. *Continued*

Type of Regimen	Reference	Subjects		Exercise Regimen(s)	Bone Measurements Site and Method	Results	Comments
		N	Age (yr)				
	Kerr et al., 1996 (116)	Tstr = 23 Tedn = 19	56 58	12 mo 3×/wk, 20–30 min, unilateral training of upper and lower limb, other side as control Strength = 3 × 8 RM; endurance: 3 × 20 RM	Radius (ultradistal, shaft), FN, Ward's triangle, trochanter, and intertrochanteric site by DXA	BMD increased significantly more in trained as compared with control site in the Tstr at Ward's triangle, trochanter, and intertrochanteric site.	Peak load was more important than the number of loading cycles in increasing bone mass. However, the volume of training was different in Tstr and Tend.
	Lord et al., 1996 (152)	T = 90 C = 89	72 69	10.5 mo, 2×/wk, strengthening, coordination, balance, and weight-bearing exercise	LS, FN, trochanter by DXA	No significant differences between groups in changes of BMD.	
	Lynch and Judge, 1992 (154)			15 mo resistance exercise and brisk walking	FN, trochanter by DXA	BMD at both sites decreased more in the exercising than in the control group.	
	Maddalozzo and Snow, 2000 (results only for women given here) (155)	Thigh = 12 Tmod = 13	53	24 wk, 3×/wk, 75 min, all muscle groups, supervised High intensity (final): 3 sets, 2–4 reps, 90+% 1 RM Moderate intensity: 3 sets, 10–13 reps, 40–60% 1 RM	Whole body, LS, FN, Ward's triangle, trochanter by DXA	No significant intergroup differences between changes of BMD.	In men training resulted in increased BMD at LS and trochanter.
	McCartney et al., 1995 (167)	T = 76 C = 66	60–80	42 wk, 2×/wk, 7 exercises, 3 sets, 10–12 reps, 50–80% 1 RM	Total body BMD and BMC, LS by DPA	No significant changes.	
	Nelson et al., 1994 (179)	T = 20 C = 19	50–70	1 yr, 2×/wk, 5 exercises, 3 sets, 8 reps, 80% 1 RM	Total body, LS, FN	BMD increased in LS (0.9%) and FN (1.0%) in T and decreased in LS (–2.5%) and FN (–1.8%) in C, difference of change significant.	
	Nichols et al., 1995 (181)	T = 17 C = 17	60–84	1 yr, 3×/wk, 8 exercises, 3 sets, 10–12 reps, 80% 1 RM	Total body, LS, FN by DXA	No significant changes of BMD.	
	Notelovitz et al., 1991 (184)	T+estr = 19 C+estr = 11	43 46	1 yr, 3×/wk, 6 exercises, 1 set, 8 reps, 8 RM	Radius by SPA, total body, spine by DPA	BMD of LS and radial midshaft increased significantly and significantly more in T+estr (+8.3% and +4.1%, respectively) than in C+estr (+1.5% and –0.3%, respectively).	
	Pruitt et al., 1995 (200)	Thigh = 8 Tlow = 7 C = 11	65–79	1 yr; high-intensity training 80% RM, low-intensity training 40% RM, both 3 sets, 14 reps, 10 exercises	LS, FN by DXA	Similar but nonsignificant pattern for the loss of LS BMD.	

TABLE 14. *Continued*

Type of Regimen	Reference	Subjects		Exercise Regimen(s)	Bone Measurements Site and Method	Results	Comments
		N	Age (yr)				
	Revel et al., 1993 (203)	T = 23 C = 26	51–71	1 yr, 2–3×/d, psoas training 60 reps/hip, 5 kg weight	Lumbar trabecular BMD by QCT	Nonsignificant decrease in BMD of C vs T.	
	Rhodes et al., 2000 (204)	T = 22 C = 22	65–75	1 yr, 3×/wk, 1 h, supervised circuit training, 3 sets, 8 reps, 75% 1 RM	LS, FN, Ward's triangle, trochanter by DXA	Nonsignificant increase of BMD in T and nonsignificant decrease in C.	
	Sinaki et al., 1989 (222)	T = 34 C = 31	49–65	24 mo, once a day, 5×/wk, weight-bearing exercises for the back	LS by DPA	BMD of LS decreased by 1.4% in T and 1.2% in C.	
	Smidt et al., 1992 (224)	T = 22 C = 27	57 55	10 mo, 3–4×/wk, 3 resistance exercises for trunk muscles, 3 sets, 10 reps, 70% of maximum strength	LS, FN, Ward's triangle, trochanter by DPA	No significant intergroup differences in changes of BMD but trend in favor of T except in Ward's triangle.	
Aerobic training regimens, NRCTs	Aloia et al., 1978 (2)	T = 9 C = 9	53 52	12 mo, 3×/wk, 60 min, conditioning exercises	Distal radius by SPA Total body Ca by neutron activation analysis	No difference in change of radius BMC between groups; total body Ca increased in T, decreased in C, difference significant	
	Bloomfield et al., 1993 (18)	T = 7 C = 7	62 59	8 mo, 3×/wk, 50 min, non–weight-bearing aerobic exercise at 60–80% HRmax, calisthenics	LS, femur by DPA	LS BMD increased by 5.3%·yr^{-1} in T and decreased by 3.7%·yr^{-1} in C, difference significant. In femur, no significant difference between changes in T and C.	
	Caplan et al., 1993 (27)	T = 19 C = 11	66 65	24 mo, 2×/wk, 60 min, weight-bearing aerobic exercise, advice to exercise ≥1×/wk extra	LS, FN by DPA	BMD of LS decreased by 0.4%·yr^{-1} in T and 1.6%·yr^{-1} in C. No significant differences of BMD changes of FN between T and C.	
	Cavanaugh and Cann, 1988 (30)	T = 8 C = 9	55 57	1 yr, 3×/wk, 15–40 min walking, 60–85% $\dot{V}O_{2max}$, progressive	LS by QCT	BMD of LS decreased in both groups at similar rate, –5.6% in T, –4.0% in C.	
	Dalsky et al., 1988 (43)	17 18	62 63	9 mo, 3×/wk, 50–60 min, walking and jogging, stairclimbing 70–90% $\dot{V}O_{2max}$	LS by DPA	BMC of LS increased by 5.2% in T, decreased by 1.4% in C, difference significant.	
	Hatori et al., 1993 (85)	Tmod = 9 Tint = 12 C = 12	58 56 58	7 mo, 3×/wk, 30 min, walking: Tmod = below anaerobic threshold, Tint: above anaerobic threshold	LS by DXA	BMD of LS increased significantly by 2.7% in Tint, nonsignificantly by 0.7% in Tmod, and C.	
	Iwamoto et al., 1998 (100)	T = 15 C = 20	65 65	12 mo, increased walking by ~45%, gymnastics 5×/wk	LS by DXA	BMD of LS increased significantly by 4.5% in T, insignificantly by 1% in C.	The subjects were osteoporotic.

TABLE 14. *Continued*

Type of Regimen	Reference	Subjects N	Subjects Age (yr)	Exercise Regimen(s)	Bone Measurements Site and Method	Results	Comments
	Kohrt et al., 1995 (122)	T = 8 C = 8	65 66	11 mo, first 2 mo flexibility exercises, then 9 mo walking, jogging, stair climbing, 3–5×/wk, 45 min, 65–85% HRmax	LS and FN, Ward's triangle, trochanter by DXA	BMD of LS and FN increased significantly by 2.7%·yr^{-1} and 3.6%·yr^{-1}, respectively, in T, no significant changes in C. Significant increase of BMD also at Ward's triangle and trochanter in T, not in C.	
	Kohrt et al., 1995 (122)	THRT = 8 CHRT = 8	66 67	Same training program as above	See above	BMD of LS increased by 8.9%·yr^{-1} in THRT by 6.6%·yr^{-1} in CHRT, and BMD of FN increased by 2.3%·yr^{-1} in THRT and in CHRT.	
	Krölner et al., 1983 (127)	T = 16 c = 15	61 61	8 mo, 2×/wk, 1 h, supervised, variety of weight-bearing aerobic and calisthenic exercises	LS, radius by DPA	BMC increased by 3.5% in T, decreased by 2.7% in C, difference significant.	
	Nelson et al., 1991 (178)	Tmod. Ca = 9 Cmod Ca = 9	60	12 mo, 4×/wk, 50 min, walking, 70–80% HRmax, mean Ca intake 761 mg·d^{-1}	LS by QCT, LS, FN by DPA	No difference in LS or FN BMD changes between Tmod Ca and Cmod Ca groups by DXA but significant increase of LS BMD by QCT in Tmod Ca.	
	Nelson et al., 1991 (178)	Thigh Ca = 9 Chigh Ca = 9	60	As above, but mean Ca intake 1462 mg·d^{-1}	As above	BMD of LS increased by 2.4%·yr^{-1} in Thigh Ca and by 0.5%·yr^{-1} in Chigh Ca; corresponding changes in FN BMD 3.0%·yr^{-1} and 0.9%·yr^{-1}, respectively.	
	Tsukahara et al., 1994 (241)	T = 30 C = 15	64	12 mo, 1×/wk, 30 min walking, jumping aerobics in water, 65% $\dot{V}O_{2max}$	LS by DXA	BMD of LS increased by 1.3% in T and decreased by 2.6% in C, changes nonsignificant.	
Aerobic training regimens, RCTs	Bassey and Ramsdale, 1995 (7)	T = 20 C = 24	**64** 55	12 mo, 1×/wk high-impact exercise + 50 heel drops·d^{-1}; in C 1×/wk low-impact exercise + flexibility exercises	LS and FN, Ward's triangle, trochanter, radius by DXA	At 6 mo, significant increase in trochanteric BMD in T, no change in C. No other significant changes.	
	Bassey et al., 1998 (8)	Tpre = 30 Cpre = 25 Tpostdepl = 45 TpostHRT = 24 Cpostdepl = 32 CpostHRT = 22	38 36 56 54 55 53	20 wk 1×/wk supervised 50 jumps during 10 min, 6×/wk the same at home, ground reaction force 3 times body weight in younger and 4 times body weight in older subjects	LS and FN and trochanter by DXA	In the premenopausal women exercise resulted in significant 2.8% increase of femoral BMD, different from C. In postmenopausal women, no significant difference between exercise and control groups after 12 or 18 mo. HRT status did not affect this outcome.	
	Bravo et al., 1996 (22)	T = 61	60	12 mo, 3×/wk, 1 h weight-bearing activities, 60–70%	LS, FN by DXA	No significant change of BMD of LS or FN in T, significant decrease of BMD at LS in C.	

TABLE 14. *Continued*

Type of Regimen	Reference	Subjects		Exercise Regimen(s)	Bone Measurements Site and Method	Results	Comments
		N	Age (yr)				
		C = 63	60	HRR + flexibility exercises			
	Ebrahim et al., 1997 (55)	Tcompl = 49 Tdrop = 32 Ccompl = 48 Cdrop = 36	66 67 68 71	24 mo, 3×/wk, 40 min brisk walking, unsupervised Compl = compliant subjects; drop = drop outs from follow-up	LS, FN by DXA	In Ccompl BMD of FN had fallen more than in Tcompl, difference 2.4%. BMD of LS had increased to a similar extent in both Tcompl and Ccompl.	
	Grove and Londree, 1992 (75)	Tlow = 5 Thigh = 5 C = 5	57 54 56	12 mo low- or high-impact activities 3×/wk, 20 min; low impacts ≤1.5 × body weight, high impacts ≥1.5 × body weight	LS by DPA	No change of LS BMD in C, 1.0% increase in Tlow and 6.9% increase in Thigh.	
	Hatori et al., 1993 (85)	Tmod = 9 Thigh = 12	58 56	7 mo; moderate intensity exercise: 3×/wk, 30 min walking at 90% of the HR at anaerobic threshold (<60% of $\dot{V}O_{2max}$); high intensity: the same at 110% of the HR at anaerobic threshold	LS by DXA	BMD LS increased by 1.2% in Thigh, decreased by 1.2% in Tlow and C.	
	Lau et al., 1992 (139)	Tcalow = 11 Ccalow = 12 Tcahigh = 15 Ccahigh = 12	79 75 76 75	10 mo, 100 × stepping up and down a 22.5-cm block, 4×/wk, upper trunk exercises	LS, FN, Ward's triangle, trochanter by DXA	Exercise had no effect on bone loss at any site, but there was significant joint effect of Ca supplementation and exercise at FN.	
	Martin and Notelovitz, 1993 (165)	T30 = 20 T45 = 16 C = 19	60 58 57	12 mo treadmill running, 3×/wk, 70–85% HRmax 30 = 30 min/session; 45 = 45 min/session	LS, proximal and distal forearm by DPA	No significant changes of BMD at any site.	
	McMurdo et al., 1997 (169)	T+Ca = 44 C+Ca = 48	60–73	6 × 10 wk during 2 years, 3×/wk, 45-min classes, weight-bearing exercise	LS by QCT	LS BMC decreased by 0.9% in T+Ca and by 2.7% in C+Ca, difference not significant.	
	Prince et al., 1995 (198)	T+Ca = 42 C+Ca = 42	63 62	24 mo, 2×/wk, 1 h, 60% HRmax, supervised weight-bearing exercise, walking 2 extra h·wk^{-1}	LS, FN, trochanter, intertrochanter by DXA	T+Ca had slightly but significantly less bone loss and FN as compared with C+Ca.	

of intensive exercise training at various ages should be studied.

The potential of PA as an osteogenic stimulus can probably be best used by combining it with the effects of hormones and drugs. The effects of various combinations of PA and drugs, hormones, and eventually other measures should be studied in order to find optimal regimens to influence bone mass and strength.

When OP is seen as a clinical condition leading frequently to fractures, the scope of the studies on the effects of PA on OP and on related dose-response issues should be enlarged to include all possible effects of PA on the risk of osteoporotic fractures.

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Physical activity dose-response effects on outcomes of depression and anxiety

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ABSTRACT

DUNN, A. L., M. H. TRIVEDI, and H. A. O'NEAL. Physical activity dose-response effects on outcomes of depression and anxiety. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S587–S597. **Purpose:** The purpose of this study was to examine the scientific evidence for a dose-response relation of physical activity with depressive and anxiety disorders. **Methods:** Computer database searches of MEDLINE, PsychLit, and Internet and personal retrieval systems to locate population studies, randomized controlled trials (RCTs), observational studies, and consensus panel judgments were conducted. **Results:** Observational studies demonstrate that greater amounts of occupational and leisure time physical activity are generally associated with reduced symptoms of depression. Quasi-experimental studies show that light-, moderate-, and vigorous-intensity exercise can reduce symptoms of depression. However, no RCTs have varied frequency or duration of exercise and controlled for total energy expenditure in studies of depression or anxiety. Quasi-experimental and RCTs demonstrate that both resistance training and aerobic exercise can reduce symptoms of depression. Finally, the relation of exercise dose to changes in cardiorespiratory fitness is equivocal with some studies showing that fitness is associated with reduction of symptoms and others that have demonstrated reduction in symptoms without increases in fitness. **Conclusion:** All evidence for dose-response effects of physical activity and exercise come from B and C levels of evidence. There is little evidence for dose-response effects, though this is largely because of a lack of studies rather than a lack of evidence. A dose-response relation does, however, remain plausible. **Key Words:** MAJOR DEPRESSIVE DISORDER (MDD), ANXIETY, TREATMENT, EFFICACY, PHYSICAL ACTIVITY, EXERCISE, REVIEW

Understanding the dose-response relation of physical activity to depression and anxiety requires consideration of several conceptual issues. Haskell concisely summarized these issues for the 1992 Second International Consensus Conference on Physical Activity, Fitness, and Health (22), and they are of considerable importance to the topic of depression and anxiety. Their consideration, described below, provides a framework to focus the content of this review and to identify future research directions.

ISSUES RELATED TO THE SPECIFICITY OF THE RESPONSE

Defining depression and anxiety. The first issue that should be considered before undertaking a review of depression and anxiety is specifically defining the response. Just as the dose-response varies for different health outcomes, it is also likely to differ depending on how one defines the desired outcomes, in this case, depression and anxiety. Experimental and quasi-experimental studies have examined effects of exercise training using various outcome measures. The participants studied have ranged from healthy individuals with few or no symptoms of depression or anxiety to individuals experiencing a clinically diagnosed disorder that could be classified as severe. Furthermore, many studies have examined the acute effects of exercise on symptoms, but such effects do not reflect the true nature of these disorders, as these illnesses are considered to be chronic and not responsive to acute treatment. Not surprisingly, this wide variation in disease severity or diagnostic criteria leads to a wide variation in responses. Consequently, for the purpose of this review, we have chosen to use standardized and specific diagnoses of depressive and anxiety disorders as outlined by *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (DSM-IV) (1). Furthermore, we have chosen to specify depression and anxiety outcomes that are likely to be ameliorated by exercise or physical activity. For example, Bipolar Disorder is thought to have a particularly strong genetic linkage that increases susceptibility to the disorder compared with other depression subtypes (20). Because of this stronger genetic link, it is unlikely that exercise alone could be an effective treatment for this disorder. Similarly, many anxiety disorders such as phobias and Posttraumatic Stress Disorder are linked to specific situations or cues (1). These disorders can be effectively treated with psychotherapy alone, and it seems unlikely that exercise could be a plausible single treatment modality. The specific definitions of depression and anxiety that have been chosen for evaluating dose-response effects should be limited to those disorders where exercise is biologically plausible.

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Criteria for diagnoses. Depression and anxiety will be defined according to the DSM-IV and the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) and ICD-10 criteria (1). Depression will include Major Depressive Disorder (MDD) (Code 296.2 or 296.3) (0–6), Dysthymic Disorder (300.4), and Depressive Disorder Not Otherwise Specified (311), but will not include Bipolar Disorder, Cyclothymia, Mood Disorder Due to a General Medical Condition, or Substance-Induced Mood Disorder. Anxiety will include Panic Disorder without Agoraphobia (300.01), Generalized Anxiety Disorder (300.02), or Anxiety Disorder Not Otherwise Specified (300.00). Other anxiety disorders such as Posttraumatic Stress Disorder, Social Phobia, Acute Stress Disorder, Agoraphobia, Obsessive Compulsive Disorder, Specific Phobias, Anxiety Disorder Due to a General Medical Condition, or Substance-Induced Anxiety Disorder will not be included.

Only studies that have evaluated the specific symptoms linked to these illnesses and include gradations of symptoms that would include at least mild to moderate levels of depression or anxiety disorders will be included in this review. Furthermore, randomized control trials (RCTs) and quasi-experimental studies will only be included if the study population has been diagnosed with the depression or anxiety disorders specified above. Depression also can be secondary to other illnesses such as cardiovascular disease, stroke, cancer, and diabetes. Similarly, other complications can arise from untreated depression such as substance abuse and alcoholism (24). These associations with other illnesses are likely to involve different or additional mechanisms that further complicate the dose-response question. To clarify issues of dose-response, it will be judicious to only review studies where depression and anxiety are the primary disorder and are not secondary to other illnesses or psychopathology.

Criteria for clinical outcomes. Another issue that is related to the specificity of the response is the way one defines the treatment response. A dose-response study of exercise as a treatment for depression or anxiety should use similar criteria to those used for established treatments of pharmacotherapy and psychotherapy. In this literature, treatment plans are linked to five key clinical outcomes. They are: 1) response and 2) remission, goals of acute phase treatment; 3) prevention of relapse and 4) recovery, goals of continuation phase treatment; and 5) prevention of recurrence, the goal during maintenance phase treatment (28,43). Response is generally operationalized and defined by clinical practice guidelines as a 50% reduction in symptoms during the acute phase of treatment. Often this acute phase of treatment lasts from 6–12 wk. There are two key points in this particular guideline that are related to dose-response. First, studies that demonstrate a statistical improvement in depressive or anxious symptoms may not always meet the accepted criterion for a treatment response. We believe this stricter criterion of a 50% reduction in symptoms should be used in establishing dose-response effects, since an improvement that is less than 50%, although statistically significant, is unlikely to be clinically relevant. Second, it is clear that amelioration of symptoms takes 6–12 wk and may not be well sustained when it occurs after a short bout of medication, psychotherapy, or exercise.

Potential etiological mechanisms. Depression and anxiety have been linked to multiple etiologies including psychological trauma and chronic stress, faulty neurotransmitter systems such as norepinephrine (NE) and serotonin (5-HT), and hypothalamic-pituitary-adrenocortical (HPA) dysfunction (11,14,34). It is highly likely that depression, like high blood pressure, has multiple etiologies, and that exercise, acting on multiple biological and psychological systems, could lead to synergistic adaptations that effectively reduce symptoms of these disorders. At the present time, the exact etiology of depression and anxiety is unknown. However, the recently released Surgeon General's Report on Mental Health documents an evolving understanding that both depression and anxiety have a biochemical basis that is found in the brain (52). For this reason, dose-response effects of exercise are biologically plausible. In fact, well-designed RCTs of nonpharmacological treatments such as psychotherapy have been shown to relieve symptoms of depression, and symptom relief is associated with neurobiological changes among treatment responders (52).

METHODS

Selection of articles for this review. A computer search of MEDLINE, PsychLit, and the Internet was conducted using combinations of the following keywords: depressive disorder, depression, anxiety, anxiety disorder, physical activity, and exercise. Next we reviewed reference lists from review articles, book chapters, and meta-analyses on exercise and depression, exercise and anxiety, and exercise and mental health. In addition, we searched our personal files and identified more than 1000 potential articles for inclusion. Articles that did not specify methods of measurement of depression or anxiety for study outcomes and that did not measure effects of exercise in depressed and/or anxious participants were excluded. Also, studies that only measured acute effects of exercise on symptoms of depression or anxiety or that measured depression secondary to other comorbid conditions and review articles were excluded. We also excluded all current meta-analyses on depression and anxiety, because the overwhelming number of studies included in the analyses of effect sizes have been performed in populations that are asymptomatic. For example, one of the most complete meta-analyses on the acute and chronic effects of exercise on anxiety included more than 100 studies. Out of these 100-plus studies, 7 were conducted in patient populations with broadly defined psychopathology, and the remainder were conducted in asymptomatic, normal populations (41). After all exclusions, the final yield was 37 articles.

TABLE 1. Cross-sectional epidemiologic studies of physical activity and depression.

Study	Population	Design/Methods	Results	Conclusion
Stephens, 1988 (49)	Four population surveys: 6913 individuals (age 25–74 yr), 23,791 individuals (age ≥15 yr), 3025 individuals (age 20–64 yr), 22,250 individuals (age ≥10 yr)	Four surveys with measures of physical activity categories (much, moderate, little/no) and depressive symptoms	CES-D depression score by amount of leisure exercise Men <40 yr: much 6.41, moderate 6.40, little/no 9.05 ($P < 0.001$) Women < 40 yr: much 9.49, moderate 9.22, little/no 12.89 ($P < 0.001$) Men ≥40 yr: much 7.56, moderate 6.91, little/no 7.38 ($P = 0.09$) Women ≥40 yr: much 8.62, moderate 8.89, little/no 11.31 ($P < 0.001$)[a]	Level of physical activity was positively associated with fewer depressive symptoms in the U.S. and Canadian populations.
Kivelä and Pahkala, 1991 (25)	Random sample of 618 men and 911 women in Finland (age ≥60 yr)	Structured interview assessing depressive symptoms, social and socioeconomic status, health, functional capacity, health behavior and losses	All: no regular exercise and depressive symptoms OR = 1.5; Men: no regular exercise and depressive symptoms OR = 1.4; Women: no regular exercise and depressive symptoms OR = 1.5	Lack of physical exercise was associated with depressive symptoms in both women and men.
Weyerer, 1992 (54)	Representative sample of 1536 males and females in Upper Bavaria (age ≥15 yr)	Structured interview assessing psychiatric disorders (Clinical Interview Schedule) Physical activity categories (regular, occasional, no)	No exercise and depression OR = 3.15 (95% CI, 1.84–5.38) Regular exercise and depression OR = 1.00 Occasional exercise and depression OR = 1.55 (0.82–2.92)	Subjects who reported no physical activity were more likely to have depressive symptoms compared with regular exercisers.
Krause et al., 1993 (27)	Random sample of 1351 males and females in Japan (mean age 68.7 yr)	Structured interview assessing physical health problems, financial strain, emotional support, negative interaction, physical exercise, depressive symptoms (CES-D)	Exercise frequency and depressive symptoms: ($\beta = -0.16$; $P < .01$)	More frequent exercise was associated with fewer depressive symptoms.
Rajala et al., 1994 (42)	Random sample of 345 males and 435 females in Finland (age 55 yr)	Postal questionnaire, interviews, and clinical examinations; depressive symptoms (Zung Self-Rating Depression Scale) and exercise categories (little, moderate, much)	Risk of depression by exercise: Men, little vs much exercise RR = 2.0 (0.7–5.8) Men, moderate vs much exercise RR = 0.7 (0.2–1.9) Women, little vs much exercise RR = 1.1 (0.4–2.9) Women, moderate vs much exercise RR = 0.9 (0.5–1.5)	Respondents who reported little or moderate amounts of exercise were not at increased risk for depression compared with individuals reporting much exercise.
Ruuskanen and Ruoppila, 1995 (44)	Representative sample of 1600 males and females in Finland born 1904–13 (age 65–84 yr) and 1914–23 (age 65–74 yr)	Structured interview assessing demographic status, social network, health status, physical activity, depressive symptoms	Intensive and regular activity was significantly associated with fewer depressive symptoms in the two youngest (65–69 and 70–75 yr) age groups	Intensive activity was related to better self-rated health, fewer depressive symptoms, and self-rated meaningfulness of life.
Penninx et al., 1999 (40)	Cohort of 6247 males and females (age ≥65 yr)	CES-D, physical disability Physical activity categories (low, moderate, high) at 4 time points Baseline data from 6-yr prospective study	Percentage of respondents who were not depressed by level of physical activity: low, 7.1%; moderate, 45.4%; high, 47.5% Percentage of respondents who were depressed by level of physical activity: low, 14.4%; moderate, 50.8%; high, 35.7% High activity: not depressed vs depressed $P < 0.001$	Respondents who reported high levels of physical activity were less likely to be depressed at baseline.
Bhui and Fletcher, 2000 (5)	Sample from the Health and Lifestyle Survey	Questionnaire measuring anxiety and depression Physical activity (minutes per day)	92–161 min·d^{-1}: OR = 0.57 (0.37–0.87), $P < 0.01$ 162–554 min·d^{-1}: OR = 0.65 (0.43–0.97), $P < 0.05$	Men who exercised at least 92 min·d^{-1} had less common depression and anxiety states. No effect was found for women.
Hassmen et al., 2000 (23)	Random sample of 3403 males (1547) and females (1856) in Finland (age 25–64 yr)	Beck Depression Inventory (BDI) Frequency of exercise (daily, 2–3×/wk, 1×/wk, 2–3×/mo, a few times per year, cannot exercise)	Exercise frequency was associated with depressive symptoms ($F = 8.5$, $P < 0.001$)	Individuals reporting less frequent exercise had more depressive symptoms.

[a] Reporting only CES-D data from the NHANES I survey. Analyses from other surveys using less accepted measures of depression were consistent with these results.

TABLE 2. Prospective epidemiologic studies examining physical activity and depression.

Study	Population	Design/Methods	Results	Conclusion
Farmer et al., 1988 (49)	Representative sample of 1900 healthy men and women in U.S. (age 25–77 yr)	Cross-sectional and prospective (8-yr follow-up): CES-D Self-report recreational and nonrecreational physical activity categories (little/no, moderate/much)	*Depressive symptoms at baseline*: Little/no vs moderate/much recreational activity: white men OR = 2.2 (95% CI, 1.2–4.2); black men OR = 16.5 (2.1–128); white women OR = 1.7 (1.1–2.5); black women OR = 1.2 (0.3–4.1) Little/no vs moderate/much nonrecreational activity: white men OR = 1.1 (0.4–2.7); white women OR = 2.1 (1.1–4.0); black women OR = 19.2 (2.3–160). *Depressive symptoms at follow-up by baseline depression*: Little/no vs moderate/much recreational activity: white men w/few symptoms OR = 1.3 (0.5–3.1); white men w/more symptoms OR = 12.9 (1.7–98.9); white women w/few symptoms OR = 1.9 (1.1–3.2); white women w/more symptoms OR = 2.0 (0.8–14.5)	White respondents who reported little or no recreational activity had twice the odds of depressive symptoms at baseline. White women with few symptoms at baseline who engaged in recreational activity were less likely to have depressive symptoms at follow-up. Small sample size and lack of follow-up data limit conclusions regarding effects of activity on depressive symptoms for black men and women.
Camacho et al., 1991 (54)	Selected sample of 1799 men and women (age ≥20 yr)	Cross-sectional and prospective (18-yr follow-up) Self-report of depressive symptoms and physical activity categories (low, moderate, high)	*Depression by activity in 1974*: low vs high activity OR = 4.22 (3.17–5.62), moderate vs high activity OR = 2.14 (1.61–2.86) *Depression in 1974 by activity in 1965*: men, low vs high activity OR = 1.76 (1.06–2.92); men, moderate vs high activity OR = 1.46 (0.91–2.34); women, low vs high activity OR = 1.7 (1.06–2.7); women, moderate vs high activity OR = 1.0 (0.63–1.59)	Low activity levels at baseline were associated with increased risk for depression at follow-up. Respondents who were inactive in 1965 but reported increased activity in 1974 were not at higher risk for depression compared with respondents who were active in 1965 and 1974.
Stewart et al., 1994 (51)	Cohort of 1758 males and females with chronic medical conditions (mean age 56.1 yr)	Prospective (2 yr follow-up) Self-report physical activity, other health behaviors, functioning and well-being, and disease and comorbidity	At 2-yr follow-up, depression was associated with perceived activity level, total time spent exercising, and total time spent walking ($P < 0.05$)	Increased physical activity was associated with better health.
Paffenbarger et al., 1994 (39)	Cohort of 21,596 college alumni (age 35–74 yr in 1962 or 1966)	Prospective (23–27 yr follow-up) Self-report physical activity (estimated kcal·wk^{-1}) Self-report physician-diagnosed depression	Physical activity index in 1962 or 1968 and risk of depression in 1988: <1000 kcal·wk^{-1} RR = 1.00; 1000–2499 kcal·wk^{-1} RR = 0.83; 2500+ kcal·wk^{-1} RR = 0.72 ($P = 0.008$)	Risk of depression was lower for individuals reporting higher levels of physical activity.
Foreyt et al., 1995 (18)	Sample of 381 normal-weight and obese men and women (mean age 44.1 yr)	Prospective (4-yr follow-up): CES-D, Eating Self-Efficacy Scale, General Well-Being Schedule Self-reported recreational activity and perceived importance of activity at 2 time points	Change in physical activity and depression for normal weight respondents ($P \leq 0.05$): lowest quartile (decreased exercise) 3.1; 2nd quartile (decreased exercise) 0.8; 3rd quartile (increased exercise) −0.9; highest quartile (increased exercise) −0.3. Correlation between change in depression and change in physical activity: normal weight −0.17 ($P \leq 0.05$), obese 0.11 (NS)	Normal weight respondents who reported an increase in physical activity exhibited fewer depressive symptoms at follow-up.
Mobily et al., 1996 (36)	Cohort of 2084 males and females (age ≥65 or older)	Cross-sectional and prospective (3-yr follow-up): modified CES-D Self-report of walking frequency (daily walking vs less frequent walking)	Baseline depression by walking status: walkers vs nonwalkers OR = 0.825 (0.64–1.06) Follow-up depression by walking status and baseline depression: few depression symptoms and daily walking OR = 1.11 (0.77–1.6); more depression symptoms and daily walking OR = 0.38 (0.18–0.79)	For individuals reporting more depressive symptoms at baseline, daily walkers were more likely to improve their scores at year 3.
Cooper-Patrick et al., 1997 (10)	Cohort of 690 male and 62 female medical students (classes of 1948–1964)	Prospective (15-yr follow-up) Self-report physical activity (change in activity, number of sweats per week) Self-report of clinical depression and review of medical records, and psychiatric distress (General Health Questionnaire)	Cumulative incidence of depression 6.4% at follow-up; risk of depression through 1993 by physical activity in 1978: *Number of sweats per week*: 0×/wk vs 3×/wk RR = 1.18 (0.53–2.64); 1–2×/wk vs 3+ ×/wk RR = 1.08 (0.48–2.45) *Change in activity from medical school*: Inactive vs remained RR = 0.86 (0.33–2.24); became vs remained RR = 0.66 (0.27–1.65)	Individuals who reported little or no exercise were not at increased risk for depression compared with those who reported exercising to a sweat at least 3 times per week. No increased risk for depression for those who were inactive or who became active relative to those who remained active.

TABLE 2. *Continued*

Study	Population	Design/Methods	Results	Conclusion
Morgan and Bath, 1998 (37)	Representative cohort of 1042 men and women in U.K. (age ≥65 yr)	Prospective (8-yr follow-up): depressive symptoms measured by Symptoms of Anxiety and Depression (SAD) scale, measured physical activity, general health, and social activity (BASE) at 4 time points	Outdoor/leisure activity at baseline and depression at 4-yr follow-up: OR = 0.92 (0.85–0.99)	Baseline level of outdoor/leisure physical activity was associated with a slight reduction in risk for depression at follow-up.
Lampinen et al., 2000 (29)	Cohort of 663 older men and women from Finland (age ≥65 yr)	Prospective (8-yr follow-up): RBDI (modified version of Beck's depression scale) Physical activity categories by increased, maintained, or decreased intensity (necessary chores, regular walking, strenuous exercise)	Change in physical activity type and depressive symptoms at 8-yr follow-up by baseline activity level: necessary chores (remained vs increased) OR = 0.96 (0.25–3.7); regular walking (decreased vs increased) OR = 10.56 (2.35–47.4); regular walking (remained vs increased) OR = 2.21 (0.53–9.3); strenuous exercise (decreased vs increased) OR = 1.23 (0.32–5.03)	Low levels of physical activity predicted depressive symptoms especially for those who reduced their intensity of activity type. Levels of physical activity at baseline predicted depression after adjusting for SES and physical function.

RESULTS

Dose-response effects of total amount of leisure-time and occupational physical activity effects on symptoms of depression and anxiety (Evidence Category C). There are nine cross-sectional and nine prospective studies (Tables 1 and 2) that examined the relation of varying amounts of leisure-time and occupational physical activity on levels of depression and anxiety, and these yield similar results across cultures. In a North American sample, Stephens (49) conducted cross-sectional analyses of data combined from surveys conducted in the United States and Canada and found that higher levels of physical activity were associated with little or no symptoms of anxiety and depression. In individuals performing moderate amounts of physical activity, there was a decrease in depressive symptoms, and this was particularly true for women and older populations. Similarly, cross-sectional analyses in a German sample (54) of 1536 men and women found those who reported no physical exercise were 3.15 times more likely to have moderate to severe depression. The odds ratio (OR) for those who reported occasional exercise was also elevated (1.55), but this was not statistically significant. Kivelä and Pahkala (25) and more recently Ruuskanen and Ruoppila (44) found similar results in a population of older adults in Finland. Even though the results of cross-sectional studies are generally consistent, the findings for men and women sometimes differ. Also, it is not clear from these analyses whether physical inactivity leads to depressive symptoms, whether depressive symptoms lead to inactivity, or whether it is a third factor such as social support that might mediate this relation. Prospective studies can help determine the direction of this relation by examining whether low levels of physical activity predict development of depressive symptoms or whether increasing physical activity can reduce depressive symptoms.

Several prospective studies have examined the temporal relation between physical activity and depression to determine if low levels of activity predict future depression. Farmer et al. (16), using survey data from the National Health and Nutrition Examination Survey (NHANES I), found low levels of leisure activity at baseline did predict depression 8 yr later in white women despite depressive symptoms being low at the time of the baseline examination. These findings remained after adjusting for age, other chronic illness, education, employment, and income. The same relation did not hold for men with few symptoms of depression at baseline; however, low levels of physical activity did predict depression in men who had depressive symptoms at the baseline examination. The Alameda County study (8) showed a similar inverse relation. Comparing active to inactive respondents at follow-up and adjusting for sex, health, and age, the ORs for depression were 1.8 for men and 1.7 for women. However, a German study did not find low baseline physical activity to be a risk factor for developing depression at 2 yr (54). A later study of male and

TABLE 3. Quasi-experimental and experimental studies examining the efficacy of exercise as a treatment for depression.

Study	Study Design and Sample	Treatment and Comparison Group	Diagnosis Type and Instrument	Depression and/or Anxiety and Fitness Treatment Outcome	50% Decrease in Symptoms
Morgan et al., 1970 (38)	Pre-post between-group design; 6 wk treatment in one of five treatment groups (circuit, jog, swim, lab, control). N = 101 men (age, 26–55 yr) APT	AT 3×/wk, 85% HRmax AT1 30–45 min (N = 18); AT2 30–45 min (N = 23), AT3 30–45 min (N = 27), AT4 10–20 min (N = 17), WLC Sole	Zung Self-Rating Depression Scale (SDS) score ≥ 50 indicating depression; 11 subjects scored ≥50 at pre-test	Participants who were depressed at the onset of study experienced a decrease in depressive symptoms after 6 wk of physical activity (SDS 51.45–44.45, P < 0.01).	No
Greist et al., 1978 (21)	Repeated measures design (12 wk treatment; 3-wk follow-up); random assignment, N = 28 men and women (age, 18–30 yr) APT/FUP	AT 3×/wk (N = 10) vs time-limited PSY (N = 6) and time-unlimited PSY (N = 12) Sole	Minor depression as determined by Symptom Checklist-90 (SCL-90) score ≥50 and Research Diagnostic Criteria (RDC) (49)	Running was as effective in reducing symptoms as both PSY. At 12 wk, running and time-limited PSY showed a greater reduction in symptoms than time-unlimited therapy PSY. 3-wk follow-up showed continued reduction in symptoms in AT.	Yes
Conroy et al., 1982 (9)	Repeated measures design; 6-wk treatment, N = 17 men (mean age, 25.5 yr) APT	AT 3×/wk (N = 9) vs AT ≤1×/wk (N = 8) Adjunct	Beck Depression Inventory (BDI), Self-Assessment Scales	Participants in the 3×/wk exercise group had a reduction in depressive symptoms (BDI 19.9–13.9) compared with ≤1×/wk exercise group (BDI 19.9–20.7).	No
Doyne et al., 1983 (12)	Multiple baseline design across subjects; 6-wk treatment; N = 4 women grouped in 2 pairs (age, 19–24 yr) APT	Multiple baseline measures were attention placebo 3×/wk until one pair group in treatment showed improvement; active treatment was 4×/wk interval training sessions for 30 min for 6 wk Sole	Major depression as measured by 2 raters according to RDC obtained by using Schedule for Affective Disorders and Schizophrenia interview (15)	Exercise decreased symptoms of depression as measured by BDI (mean change scores from baseline to treatment of 14, 16.9, 15.2, 11.3) and Depression Adjective Check List (DACL). Treatment gains maintained at 3-mo follow-up.	Yes
Martinsen et al., 1985 (32)	Repeated measures design for 9 wk in men and women (age, 17–60 yr) APT	AT (50–70% max. aerobic capacity) 1 hr/3×/wk + PSY (N = 28; 9 on PHM) vs PSY (N = 21; 14 on PHM) Adjunct	DSM-III criteria for major depression (1) Level of depression assessed by Comprehensive Psychological Rating Scale (CPRS) (2) and BDI (4)	Both groups significantly decreased depression scores, and exercise training group had significantly larger effect. Also, increase in aerobic power inversely correlated with reduction of symptoms. A later report (31) showed 50% in exercise group continued to exercise and had significantly fewer depressive symptoms.	Yes
Klein et al., 1985 (26)	Pre-post between-group design; 12 wk of treatment with follow-up to 9 mo; random assignment of men and women (mean age, 30 yr) APT/FUP	AT 45 min/2×/wk (N = 27) and PSY (N = 24) vs PHM (N = 23) Sole	Diagnosis of major or minor depression and receiving no other treatment (RDC) and SCL-90 (15)	All groups significantly reduced symptoms at 12 wk. There was no difference between groups at 12 wk. Symptoms were still reduced at 9 mo.	Yes
Sime and Sanstead, 1987 (46)	Multiple baseline with repeated measures design; 4 wk baseline, 10 wk treatment; men and women (age, 26–53 yr) APT/FUP	AT 4×/wk for 21 mo (N = 15) Sole	Moderate depression assessed by BDI (4)	Significantly decreased at 6 and 21 mo follow-up; 13 participants completed follow-up measures (9 of 13 reported continuing exercise).	No
Doyne et al., 1987 (13)	Repeated measures design (baseline, 1 mo, 7 mo, and 12 mo); 8 wk treatment; N = 40 women matched on baseline BDI and randomly assigned to 1 of 3 groups (age, 18–35 yr) APT/FUP	AT 4×/wk using ACSM guidelines and RT 4×/wk below 50–60% max HR vs WLC for 8 wk Sole	Diagnosis using RDC criteria, measured BDI, DACL, Hamilton Rating Scale for Depression (HRSD), and fitness	Significant decrease in depression in two exercise groups compared with wait list control measured by BDI, HRSD, and DACL. Symptoms were still reduced at 1 mo, 7 mo, and 12 mo. Neither exercise group increased fitness. There was no significant difference in attrition.	Yes
Fremont and Craighead, 1987 (19)	Repeated measures (10 wk treatment; 2 mo follow-up) random assignment of men and women (age, 19–62 yr) APT/FUP	AT 20 min 3×/wk (N = 15); PSY (N = 16) vs AT 20 min/3×/wk and PSY (N = 18) Sole	BDI score between 9 and 30	All groups significantly improved by the 5th week and improvement was maintained during 2-mo follow-up BDI baseline walk/run 17 ± 6.2, counseling 19 ± 7.8, combined 18 ± 7.5; Wk five 7 ± 5.7, 9 ± 6.6, 13 ± 8.8; 2 mo 6 ± 7.0, 7 ± 6.6, 6 ± 6.5; No difference for more severe symptoms.	Yes
Martinsen et al., 1989 (30)	Pre-post randomized block by gender (38 men, 61 women); 8 wk treatment (mean age, 41 yr) APT	AT (70% $\dot{V}O_{2max}$) for 1 hr/3×/wk (N = 51) and RT (strength, flexibility, and relaxation at low intensity for equivalent time) Adjunct	DSM-III criteria for major depression, dysthymia, depressive disorder not otherwise specified (49 patients also had diagnosed anxiety disorder) (1); BDI > 9	Both groups had significant reductions in depression scores and increase in fitness was not correlated with increase in cardiorespiratory fitness; 90 of 99 completed the study (only 2 withdrew due to exercise).	No
Sexton et al., 1989 (45)	Repeated measures design (8 wk treatment, 6 mo follow-up) men and women (N = 52) randomly assigned (age, 19–60 yr) APT/FUP	AT (jog, 70% predicted HRmax) 30 min/3–4×/wk vs AT (walk, comfortable speed) 30 min/3–4×/wk Sole	Nonpsychotic DSM-III diagnosis, Symptom Checklist, State-Trait Anxiety Inventory, BDI, Global Assessment Scale	Both groups showed a similar reduction in anxiety and depression scores *Walkers*: baseline BDI 22.4 ± 7.1, 8 wk BDI 11.9 ± 10.7, 6 mo BDI 12.2 ± 9.5 *Joggers*: baseline BDI 23.0 ± 9.3, 8 wk BDI 9.8 ± 10.8, 6 mo BDI 10.2 ± 11.6 Reductions were maintained at the 6-mo follow-up. Those with greater aerobic fitness had significantly lower anxiety at follow-up.	Yes

TABLE 3. *Continued*

Study	Study Design and Sample	Treatment and Comparison Group	Diagnosis Type and Instrument	Depression and/or Anxiety and Fitness Treatment Outcome	50% Decrease in Symptoms
Steptoe et al., 1989 (50)	Pre-post between-group design matched on age, sex, body weight, activity level, and initial anxiety level; 28 women and 5 men randomly assigned to 1 of 2 treatment conditions for 10 wk; (age, 20–60 yr) APT	AT (60–65% HR_{max}) 30 min/4×/wk vs flexibility, mobility, and strength (50% HR_{max}) 30 min/4×/wk Sole	Score of 8–10 or ≥11 on the Hospital Anxiety and Depression Scale (HAD) and/or score on the tension-anxiety scale of the Profile of Moods States (POMS)	Participants in the aerobic exercise group had a decrease in tension-anxiety and depression scores on the POMS. Tension-anxiety (9.6–6.6), depression (0.77–0.58)	No
McNeil et al., 1991 (33)	Pre-post between-group design; participants randomly assigned to 1 of 3 treatments for 6 wk; (mean age, 72.5 yr) APT	AT 20–40 min (2 supervised; 1 unsupervised visits·wk^{-1}); social contact (2 visits·wk^{-1}) vs WLC Sole	BDI score within moderate range of 12–24	Both exercise and social contact decreased depressive symptoms significantly compared with wait list control (BDI exercise 16.6 ± 3.1 to 11.1 ± 3.0; social contact 16.0 ± 3.6 to 11.8 ± 4.0; wait list 15.2 ± 2.4 to 14.7 ± 3.7). Greater decrease in somatic symptoms in exercise group than social contact and wait list.	No
Veale et al., 1992 (53)	Pre-post between-group design (2 studies); 12 wk treatment; $N = 83$ (study 1) and $N = 89$ (study 2) men and women randomly assigned (age, 18–60 yr) APT	Study 1: AT 3×/wk vs control Study 2: AT 3×/wk vs low-intensity exercise (relaxation, stretching, yoga) 3×/wk Sole/Adjunct	Clinical Interview Schedule (CIS) >17 and depression severity score >2; also BDI; not all patients receiving PSY or PHM	*Study 1*: AT decreased depressive symptoms on CIS but not BDI when compared with control (no fitness improvement). *Study 2*: no difference between intensity groups; both improved on CIS and BDI.	No
Singh et al., 1997 (47)	Pre-post between-group design; men ($N = 12$) and women ($N = 20$) randomized to 1 of 2 groups for 10 wk (mean age, 71 yr) APT	High-intensity RT 3×/wk vs interactive EDC for 2×/wk Excluded if mini-mental state <23 (17) Sole	DSM-IV diagnosis of minor, major depressive disorder (mild to moderate) or dysthymia; also BDI, HRSD, and Geriatric Depression Scale (GDS) (56)	Resistance-trained group significantly reduced all depressive symptoms on all measures compared with health education controls (BDI 21.3 ± 1.8 to 9.8 ± 2.4 vs controls 18.4 ± 1.7 to 13.8 ± 2, $P = 0.002$). The intensity of training was a significant independent predictor of decrease in depression scores.	Yes
Broocks et al., 1998 (7)	Pre-post between-group design; men ($N = 23$) and women ($N = 23$) were randomized to 1 of 3 treatment conditions for 10 wk (age, 18–50 yr) APT	AT 3–4×/wk, PHM, and PHM placebo Sole	DSM-III-R diagnosis of panic disorder and agoraphobia and ICD-10 criteria	Exercise had a significant effect over placebo at 8 wk. When comparing exercise and clomipramine, clomipramine was more effective. Hamilton Anxiety Scale: Exercise 14 vs clomipramine 9.	No
Meyer et al., 1998 (35)	Repeated measures design, matched on age; men ($N = 36$) and women ($N = 37$), 1 of 3 treatment conditions for 10 wk APT	AT 45–60 min/3×/wk (panic patients), AT 45–60 min/3×/wk (controls), PHM, and PHM placebo Sole	Bandelow Panic Agoraphobia Scale self rating 25.0 SD 7.6, observer rating 25.4 SD 7.9. Hamilton Anxiety Scale 22.6 SD 7.6, Clinical Global Impression 4.4 SD 0.8	At 10 wk, exercise group (panic patients) showed significant improvement in all 4 clinical efficacy criteria compared with placebo treatment. At 4 wk, clomipramine was more effective than exercise but at 8 wk this effect almost diminished. BPAS 10 wk: exercise 15 vs clomipramine 10. Hamilton 10 wk: exercise 10 vs clomipramine 10.	Yes
Blumenthal et al., 1999 (6)	Repeated measures design; men ($N = 43$) and women ($N = 113$) randomized to 1 of 3 groups for 16 wk (age ≥ 50 yr) APT	AT 3×/wk at 70–85% HR_{max}; PHM (sertraline); AT and PHM (sertraline) Sole and Adjunct	DSM-IV diagnosis of major depressive disorder and HRSD ≥13, BDI	All treatment groups reduced depressive symptoms. HRSD baseline Exercise 17, Medication 18, Combination 17 vs 16 wk post Exercise 8, Medication 7, Combination 9. BDI baseline 20, 22, 22 vs 16 wk post 9, 8, 10 for Exercise, Medication, and Combined, respectively (numbers interpreted from graph)	Yes
Babyak et al., 2000 (3)	Repeated measures design; $N = 133$ of the original 156 participants available for assessment at 10 mo (age ≥ 50 yr) FUP	AT 3×/wk at 70–85% HR_{max}; PHM (sertraline); AT and PHM (sertraline) Sole and Adjunct	DSM-IV diagnosis of major depressive disorder and HRSD, BDI	6 months after conclusion of the treatment program BDI scores did not differ between groups: Exercise 8.9, Medication 11.0, Combination 10.6. Participants in Exercise (30%) had lower rates of depression compared with Medication (52%) or Combination (55%), with depression defined as DSM-IV diagnosis or HRSD >7.	Yes

RT, resistance training; AT, aerobic training; PSY, psychotherapy; PHM, pharmacotherapy; WLC, wait list control; EDC, education control; APT, acute phase treatment; FUP, follow-up; Sole, exercise treatment only; Adjunct, exercise and psychotherapy and/or pharmacotherapy.

female medical students also did not find an increased risk of depression attributable to being inactive at baseline or becoming inactive at a 15-yr follow-up (10).

Five prospective analyses also report whether increases in physical activity lead to reductions in depression. For example, improvements in depression scores come from observations of the Iowa 65+ Rural Health Study (36). A logistic regression analysis of 2084 men and women found those who reported more depressive symptoms at baseline and who walked every day were one third (OR, 0.38) as likely to report high a number of depressive symptoms at follow-up compared with those who did not walk. In the group who reported no depressive symptoms at baseline and who walked every day, there was no change in depressive symptoms (e.g., their depressive symptoms remained low). Paffenbarger et al. (39) also found an inverse relation between physical activity and subsequent risk of depression in the Harvard Alumni study. Men who expended 1000–2499 kcal·wk^{-1} in walking, stair climbing, and sports play were at 17% less risk of developing clinical depression than their less active peers. Men who expended 2500 or more kcal·wk^{-1} were 28% less likely to develop clinical depression. This is the only prospective study that demonstrates a dose-response gradient between amounts of physical activity and reduction in diagnosed depression. Other prospective studies examining effects of increasing physical activity on symptom reduction did not analyze any dose-response relation.

Exercise training studies: characterizing the dose in terms of intensity, duration, and frequency on depression and anxiety (Evidence Category B). Table 3 shows consistency across studies in demonstrating a reduction in symptoms of depression and anxiety with aerobic and resistance training protocols. Eight of 18 studies indicate a 50% reduction in symptoms during the acute phase treatment. Furthermore, in the seven studies that also included a follow-up or maintenance phase, this response was maintained for periods of 3–21 months. Although the results of these studies are consistent, there are limitations and design flaws in many of these studies including lack of adequate control groups, mixing of treatments (e.g., exercise is combined with pharmacotherapy or psychotherapy), and small sample sizes. Also, we were able to locate only two studies examining these effects in patients diagnosed with anxiety disorders.

We were not able to locate a single published study that has examined the combined effect of varying intensity, duration, and frequency of exercise, although some studies have compared different intensities or different frequencies. With regard to intensity, Sexton et al. (45) examined reductions in depressive symptoms and anxiety in "neurotic" inpatients assigned to either a walking treatment or a more vigorous jogging treatment. Both groups showed equal reduction in their symptoms of anxiety and depression, but the jogging group had significantly more dropouts. Veale et al. (53), who compared aerobic exercise of low intensity with higher intensity, found similar results. Both groups decreased their depressive symptoms, but there was no significant difference between groups.

In addition to the issue of exercise intensity, one study has examined the effects of two different frequencies of aerobic training on depressive symptoms. Conroy and colleagues (9) examined the effects of exercise 1 d·wk^{-1} versus 3 d·wk^{-1} over a 6-wk period and found the 3-d·wk^{-1} treatment had greater effects than the 1-d·wk^{-1} treatment. We were unable to locate any published studies in depressed patients that have examined differing durations of exercise. Future studies that examine the dose of exercise will also need to take into account total energy expenditure, because the intensity, frequency, and duration sum to total energy expenditure.

Aerobic versus resistance training and reduction of symptoms of depression and anxiety (Evidence Category B). Sixteen of the 19 studies in Table 3 used only aerobic exercise as the exercise treatment modality. Of the remaining three studies, two compared aerobic exercise with resistance training (13,30), and one examined the effects of resistance training compared with a health education control (47). Each of these three studies examining the effects of resistance training showed significant effects in reducing depressive symptoms among different aged populations.

Fitness and treatment response (Evidence Category B). Only 25% of the studies in Table 3 and none of the studies in Tables 1 and 2 measured whether improvements in cardiorespiratory fitness were associated with changes in depression. Studies that did measure changes in fitness are equivocal. For example, the first study by Martinsen et al. (32) indicated the decrease in depression was significantly correlated with the increase in cardiorespiratory fitness, whereas the later study comparing aerobic fitness and weight training exercise did not replicate this finding (30).

SUMMARY

First, with regard to the question of whether the amounts of occupational and leisure time physical activity are linked to reductions in symptoms of depression and anxiety: This evidence is generally consistent for both cross-sectional and prospective studies and findings are similar across cultures; however, these studies are only observational. Also, only two of these observational studies presented data on anxiety symptoms. Second, with regard to the question of whether varying the intensity, frequency, and duration of the exercise prescription has a dose-response effect on depression and anxiety, there is evidence to suggest that both moderate and vigorous exercise can reduce symptoms of depression. No studies have varied frequency or duration or controlled for total energy expenditure. Third, with respect to resistance and aerobic exercise, there is evidence that both can reduce symptoms of depression. However, in the studies that compared aerobic versus resistance training, it is unknown if total energy expenditure was equivalent. Fourth, it is also not clear from the exercise training

studies whether or not increases in cardiorespiratory fitness are necessary to reduce symptoms of depression. Also, with respect to all of these questions, there are more data examining depression disorders compared with anxiety disorders.

RESEARCH RECOMMENDATIONS

The questions posed for this review suggest several lines of research to understand dose-response effects of exercise and physical activity on the treatment and management of depression and anxiety disorders. In all of these future research efforts, studies should follow criteria established for treatment studies in terms of adequately diagnosing patients and using outcome measures with appropriately defined treatment standards. Until this becomes the accepted practice, rather than the exception, little progress will be made with regard to understanding exercise as a treatment modality for either depression or anxiety. Furthermore, future studies should carefully document the exercise dose and examine the relation of treatment outcomes with cardiorespiratory and/or muscular fitness.

1. Prospective observational studies should be conducted to determine whether increasing the frequency, intensity, or duration of physical activity is associated with symptom reduction of depression and anxiety. Furthermore, it will be important to compare various subgroups in these analyses (e.g., comparing older with middle-aged and younger persons, comparing men with women, and comparing different ethnicities).
2. Prospective observational studies also are needed to examine the relation between cardiorespiratory fitness and symptoms of depression. Again, it will be important to examine the influence of age, gender, and ethnic subgroups.
3. RCTs are needed to examine the effect of types of exercise as well as frequency, intensity, and duration on various subtypes of depression and anxiety. Future trials also should examine whether different doses of exercise can be a sole treatment or should be implemented as an adjunct treatment depending on depression or anxiety severity and subtype.
4. To clarify issues related to intensity of exercise and physical activity, it will be important to examine effort sense (rating of perceived exertion) for both relative and absolute exercise intensities in patients with different subtypes of depression and anxiety.
5. RCTs examining biological and psychological mechanisms in relation to exercise dose and treatment effects need to be conducted. Examples of mechanisms to be investigated include brain imaging studies similar to those conducted for antidepressant drug studies, effects on HPA axis function, or neurotransmitter regulation.
6. Because both resistance training and aerobic exercise have demonstrated similar effects, it will be important to explore possible mechanisms that these different types of exercise share (e.g., changes in vagal tone or neurotransmitter modulation), and the relation to possible treatment effects.
7. Dose of exercise also needs to be examined with respect to the other phases of the illness, in addition to the acute phase treatment. For example, how many weeks of exercise are needed for a full remission? Can different types of physical activity and/or exercise prevent recurrence?
8. Finally, exercise may have its greatest impact on prevention of depression. Population studies are needed to evaluate this question. Also, RCTs should be conducted to examine the effects of exercise on recurrence of depression or anxiety disorders, particularly during continuation or maintenance phase treatment.

CONCLUSION

All evidence for dose-response effects of physical activity and exercise comes from Evidence Category B and C levels. Cross-sectional data from observational studies consistently demonstrate that physical activity is associated with reduced symptoms of depression, but there is less evidence for reduced symptoms of anxiety. Data from prospective studies are more equivocal. Furthermore, there is only one prospective study that has examined the dose-response question with respect to depression. Clearly, more observational studies are needed to evaluate the potential for prevention of clinical illness. Evidence from quasi-experimental studies and RCTs also consistently demonstrates a reduction in symptoms of depression attributable to both aerobic and resistance exercise. Again, there are fewer quasi-experimental studies and RCTs in patients diagnosed with anxiety disorder. Additional RCTs are needed to examine dose-response of exercise as both a sole and adjunct treatment in different subtypes of depression and anxiety and in various subgroups. Also, RCTs are needed to explore the possible underlying biological and psychological mechanisms of treatment effects. At this point the evidence is suggestive but not convincing.

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Exercise dose-response effects on quality of life and independent living in older adults

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ABSTRACT

SPIRDUSO, W. W., and D. L. CRONIN. Exercise dose-response effects on quality of life and independent living in older adults. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S598–S608. **Purpose:** The purpose of this study was to determine if exercise operates in a dose-response fashion to influence well-being and to postpone dependency. **Methods:** A computer-assisted search was made by using the following key words: resistance training, strength training, function, exercise, elderly, quality of life, frailty, physical activity, independence, performance, aerobic training, mobility, well-being, and disability. Review articles and personal files were also used, and a critical review of research studies meeting the criteria described in the methods section of the article was conducted. **Results:** In large sample correlational studies and prospective longitudinal studies, researchers consistently report that measures of physical function in old adults are related to feelings of well-being, and that old adults who are physically active also report higher levels of well-being and physical function, but the results of randomized intervention studies of aerobic and/or resistive strength training do not always support this relationship. Even if changes in well-being and physical function were reported, no evidence was found that levels of intensity operated in a dose-response fashion to influence these changes. Research design problems included ineffective aerobic or strength training treatments, widely varying participation and effort of the research participants, and both treatment and physical function tests that were not appropriate for the physical status of the participants. **Conclusion:** The most consistent results were that long-term physical activity is related to postponed disability and independent living in the oldest-old subjects. Even in individuals with chronic disease, systematic participation in physical activities enhances physical function. **Key Words:** PHYSICAL FUNCTION, PHYSICAL ACTIVITY

INTRODUCTION AND METHODS

Quality of life of older adults. Successful aging, (1–65) or maintaining a high quality of life, was proposed by Rowe and Kahn (47) to be composed of three aspects: freedom from disease, engagement with life, and physical and mental competence. High quality of life means that individuals feel better, function better on a daily basis, and for most, live independently. In this article, quality of life is defined by the conceptual framework proposed by Stewart and King (54), and shown in Table 1. In this framework, health-related quality of life is composed of two major domains: functioning (physical, cognitive, and social), and well-being (perceptions of health, emotional function, and self-concept). Quality of life is subjective, and the value of various components differs not only among individuals but within individuals at different stages of life.

The question at hand is whether exercise and/or physical activity (PA) can contribute substantially to an enhanced quality of life for adults who are 65 yr or older, and if so, what levels are necessary to be effective. The goals of exercise and PA are different for young and old adults. For younger adults, exercise is recommended to prevent cardiovascular disease, cancer, and diabetes, and to increase life expectancy. But it is hoped that exercise and PA for the oldest adults can combat the frailty and vulnerability that are caused by inactivity, minimize the biological changes of aging, reverse disuse syndromes, control chronic diseases, maximize psychological health, increase mobility and function, and assist with rehabilitation from acute and chronic illnesses (32).

Methodological limitations in studies of quality of life and dose-response concepts. Just as the goals of exercise are somewhat different for older adults, the concept of applying exercise dose-response paradigms developed for young adults to those in their 70s and 80s has some difficulties. First, although frequency, duration, and modality can be directly observed and quantified, assessing exercise intensity is problematic in very old adults. High intensities of a dose-response range are associated with health risks and sometimes pain. Second, many physical characteristics other than aerobic capacity, such as denture problems, muscle cramps, loss of tissue pulp in the fingers and soles of the feet, or peripheral neuropathies may preclude accurate measurement of the fitness or strength of older adults. Third, the energy cost of activities with assistive devices (walkers, wheelchairs), joint deformities, and gait disorders may be significantly higher than standard equations would predict (32). Fourth, PA may enhance the quality of life without improving cardiorespiratory status. Just the frequency of exercising may be beneficial in and of itself (54). For example, mood, pain,

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TABLE 1. Health-related quality of life framework.[a]

I. Functioning domains
- A. Physical functioning
  - Aerobic fitness, strength, muscular endurance, balance, flexibility
  - Physical tasks for daily function—walking, chair-rise, stair-climb bending, lifting, stooping, carrying heavy objects, running, hand function
- B. Cognitive functioning: memory, attention, concentration, comprehension, problem solving
- C. Engagement with life activities:
  - Self-maintenance activities—ADL, IADL
  - Role activities—societal obligations and connections
  - Social activities—social groups, community gatherings
  - Hobbies, recreation
- D. Objective health measures (disease symptoms)

II. Well-being domains (subjective, internal states)
- A. Bodily well-being—feelings about symptoms and bodily states, presence of pain, disease, energy/fatigue, sleep disturbance
- B. Emotional well-being—positive and negative feeling states (depression, anxiety, anger/irritability, positive affect)
- C. Self-concept—positive and negative perceptions about oneself (self-esteem, sense of mastery/control)
- D. Global perceptions of well-being—summary ratings and evaluations
  - Health—personal beliefs and evaluations of health in general "How do you rate your health overall?"
  - Life satisfaction—contentment with current life; congruence between desired and achieved states

[a] Modified from Stewart, A. L., and King, A. C. Evaluating the efficacy of physical activity for influencing quality-of-life outcomes in older adults. *Ann. Behav. Med.* 13:111, 1991.

stiffness, and fatigue may be enhanced by yoga (40). Thus, many researchers have turned to self-report of PA behavior as an alternative to differentiate older adults who may have higher levels of cardiorespiratory capacity, muscular strength, and flexibility as a result of their activity.

The quantification of quality of life is equally fraught with difficulties. Many of the instruments used to assess quality of life have only moderately high reliabilities and uncertain validities. Some are single-item measures, such as, "My health is 'better than,' 'the same as,' or 'worse than' that of other people my age." Many tests require participants to judge the amount of change in a variable that they think they have experienced. Response bias and cohort differences are problems in items of recall and self-report. Perceptions of intensity are different in older cohorts. Nevertheless, the concept of well-being refers to the way people *feel* about their life, and investigators have found few ways to study this without simply asking the participants how they feel.

Evidence selection criteria. A large body of literature exists regarding the relationship of exercise to each of the quality-of-life components shown in Table 1, and a review of all of these would be prohibitive. Therefore, the studies included in this analysis meet the following criteria: a) participants are over 65 yr of age; b) the purpose is to relate different levels of PA or fitness parameters to quality of life outcomes or to disability and dependent living; and c) both quality of life domains, "functioning" and "well-being," are represented by two or more outcomes. Studies of PA and physical function as the only outcome measure were also included because ". . . a wide variety of behavioral, social, psychological, health status, and demographic risk factors are associated with changes in physical functioning" (27), and it is thought to be composed of several abilities that form the foundation for independent living.

CURRENT STATUS OF KNOWLEDGE

Exercise, physical activity, and well-being. On the basis of nonrandomized cross-sectional correlational studies, researchers consistently report that measures of physical function in the elderly are related to feelings of well-being (20,37,64). Physical function is an important predictor of social support (64) and predicts the number of face-to-face contacts and the number of sources of instrumental support that older adults have (2) (Evidence Category C). In large prospective studies, both nonrandomized (Table 2) and randomized (Table 3), PA status appears to be related to levels of well-being (40,56,58). Some evidence is available that active older adults have fewer depressive symptoms, but only for the young-old (60–75 yr) and not the oldest-old (76+ yr) (49). Older adults who enthusiastically participated in community-based fitness and sports classes and who adopted a new PA and maintained it for 6 mo reduced anxiety and depression symptoms and increased self-esteem (56). The mirror image of that observation is that older adults who feel good about their emotional functioning may exercise and be more active (31). The evidence for a linkage of PA levels to well-being (36), life satisfaction (56,59), or to measures of control or mastery (51,56), is not always positive (Evidence Category C).

In nonrandomized or uncontrolled studies in which an exercise intervention was applied (Table 4), evidence for a training effect on aspects of well-being was weak. No changes in well-being were reported after 6 mo (11), 9 mo (59), or 1 yr (55). When changes were reported, they were small (9) and occurred only when participants were regrouped *post hoc* on the basis of the percent of time spent in the training zone (14) (Evidence Category C). Exercise effects on components of well-being were also mixed in the only two randomized control experiments available (Table 5). King (28) reported significant differences in well-being, and in the participants' confidence of their physical function, after 12 mo, but not 6 months of community-based PA classes. Peel (38) also reported participants' confidence to be increased, and their emotional function to improve. Conversely, Perrig-Chiello et al. (39) found no improvement or training group differences in well-being, self-efficacy, or control beliefs after 8 wk of resistive training (Evidence Category B). No studies were found that could be categorized as Evidence Category A.

In summary, correlational studies support a relationship between PA and components of well-being, evidence from intervention studies is mixed, and no evidence from truly experimental studies (Evidence Category A) is available. Finally, although almost all investigators assume that habitual exercise may improve psychological well-being, and some intervention studies document this, it may also be true that a strong sense of well-being is necessary to comply with a habitual and intensive exercise program (49).

Exercise, physical activity, and physical function. Within the health-related quality of life framework, physical function has two components: the physical attributes and capacities underlying movement (cardiorespiratory fitness,

TABLE 2. Physical activity and quality-of-life indicators in nonrandomized, large samples.[a]

References	Participants	Physical Activity Levels	Study Design	Physical Function	Cognitive/Engagement with Life	Health Status Disease	Well-Being
McPhillips et al., 1989 (31)	508 M 66.5 yr 632 F 67.0 yr Range, 50–93 yr Com living Volunteers	Amount of Light Moderate Heavy exercise/wk of Ps who rated QL factors as: Better/Same Worse (than others, exercise weighted by frequency and intensity)	Retrospective Descriptive student's *t*-test, age-adjusted rates by direct method (using sample as standard), data base acquired 1984–1987	Those who *perceived* their physical function as less limited exercised almost twice as much as those who did not Moderate and heavy exercisers were few, and were not different than light exercisers on function		Those who rated their health as Better/Same exercised almost twice as much as those who rated their health as Worse than others; moderate and heavy exercisers were few, and were not different than light exercisers on health	Those who felt better about their emotional functioning exercised almost twice as much as those who did not Moderate and heavy exercisers were few, and were not different than light exercisers on emotional control
Mor et al., 1989 (33)	Not intact = 248 M, 528 F Intact = 448 M, 513 F 70–74 in the LSOA 1984 Com living	Walking Self-reported existence of a regular exercise routine Self-report; walk at least 1 mile, 4–7 days·wk Have a regular exercise routine	Multivariate logistic regression Outcomes: Relative risk of decline in indicators 2 yr later (1986)	Those without an exercise routine were 1.5 times more likely to decline; those who never walk at least 1 mile·wk were 1.56 times more likely to decline in function and become unable to do ADLs and IADLs			
Seeman et al., 1995 (51)	1015 M and F 70–79 yr Com living; highest ⅓ functioning cohort MacArthur Studies of Successful Aging	PA groups: Any PA None On the basis of self-report of leisure and work-related PA 90-min interview	Regression to predict change in performance from 1988–1991, for adults differing in activity level; 2.5 yr follow-up in 1991 of 1998 performance	Participation in moderate *or* strenuous activity associated with positive changes in balance, gait, chair-stand, foot tap; independent of sociodemographic and baseline health status	Emotional support from social network marginally predicted physical performance ($P = 0.07$)		NS: Self-efficacy in 9 domains Personal mastery Life satisfaction Happiness
Strawbridge et al., 1998 (57)	M 247, F 327 65+ 85+ Com living Alameda County, CA	Self-report exercise groups: Often Sometimes Never did (Long walks, swim, active sports); also Frail Not Frail	Longitudinal, regression Estimate impact of cumulative predictors Estimated impact of frailty on QL 30 years, 3 waves of data collection: 1965, 1974, 1983, 1994	Likelihood of frailty over the 3 waves of study: OR = 1.95 for physically inactive	NS: Cognition Feeling socially isolated	Fair/poor perceived health: OR = 4.08 for frailty Chronic symptoms: OR = 2.56	"Not-frail" had more life satisfaction, enjoyed free time, felt loved, satisfied with relationships, mental health, well-being

ADL, activities of daily living; Com living, community living; OR, odds ratio; IADL, Instrumental Activities of Daily Living; LSOA, Longitudinal Study of Aging; NS, not significant; Ps, participants; PA, physical activity; QL, quality of life.
[a] Dose-response: physical activity levels (Evidence Category C).

TABLE 3. Physical activity and quality-of-life indicators in large, randomized samples.[a]

References	Participants	Physical Activity Levels	Study Design	Physical Function	Cognitive/Engagement with Life	Health Status Disease	Well-being
Brown et al., 2000 (6)	14,502 18–23 yr 13,609 45–50 yr 11,421 70–75 yr Women selected from Medicare insurance base Com living	PA score of frequency and weighted on intensity; 0–80 self report	Regression of 3 subscores of SF-36 (mental health, general health, and vitality) on exercise PA score		Mental health measures increased sharply with increasing PA scores from 0–10, then leveled off for remainder of the PA scores.	SF-36 subscale vitality scores and general health scores continued to rise with increasing PA from scores 0 to 40 and then leveled off.	Among older women, SF-36 increased with increasing PA scores; in older women, a sharper increase in SF-36 scores with PA scores from 0–10. Highest vitality and mental health scores seen among older women.
Simonsick et al., 1993 (52) EPESE	65–74 yr olds M 1582 F 2045 75+ yr olds M 682 F 868 T 2264, 2913 Com living unimpaired	Ps grouped into High Moderate Inactive Recreation and home PA, not work	Prospective, longitudinal with assessed outcomes at 3 and 6 yr Detailed in-person interviews OR	In high-PA group all ORs associated with physical impairment (1/2-mi walk, <1.0); graded response between PA and impairment		PA related to health (MI, stroke, diabetes, angina) High PA reported better self-rated health, lowest chronic diseases.	High PA reported lowest depression scores.
Reubin et al., 1990 (45)	M F 1. 103 292 2. 59 104 3. 40 34 4. 25 30 T. 227 260 M = 77.7 yr Com living	P grouped *post hoc* as: 1. No exercise 2. Short walk 3. Frequent long 4. Frequent vigorous Self-exercise reported walking, jogging, sports activities	Baseline and 1-yr follow-up. Ps grouped: improved, declined, no Δ in physical AADL, MANOVA of change scores and repeated measures	Exercise levels correlated positively in a graduated manner with AADLs		Exercise levels correlated positively in a graduated manner with current health status.	Changes in exercise level in both directions were correlated with changes in mental health status.
Ruskanen and Ruoppila, 1995 (49) Evergreen Project	M 419, F 805 65–84 yr Com living	Ps grouped as: Intensive Regular training, daily activities (self-ratings)	From 2 random samples of 1000, 77–86 yr and 87–96, *post hoc* comparison groups and LISREL		NS: All cognitive indicators.	Exercisers > nonexercisers on self-rated health.	Exercisers > nonexercisers on self-rated meaningfulness of life, and on depressive symptoms only for age groups 65–69 and 70–75 yr.
Ratanan et al., 1999 (43) WHAS	1002 65+ yr Com living	Ps grouped as: 0 = inactive 1–3 = minimally active >4 = moderately active	Prospective, population study Cross-sectional MANOVA LISREL	Both PA and strength were predictors for severity of disability LISREL: PA → strength → disability Spiraling model of decline in which strength has a significant role		Multiple diseases associated with a greater degree of motor disability. Number of chronic diseases and knee pain associated with motor disability; model R^2 explained 22% of variation in motor disability, 27% of PA, 11% of knee extensor strength, and 23% of hand grip.	
Young et al., 1995 (65)	3640 M 71–93 yr Honolulu Heart Program, baseline 1988, Com living and in institutions	Ps grouped as: Low, medium, and high daily EE; self-report and performance-based physical function	Population-based longitudinal, multiple logistic regression, chronic diseases, 1988 and 3- to 5-yr follow-up for physical function assessments.	High-EE Ps more likely to have optimal function in ADL, IADL, physical endurance-type tasks than low-EE group. Linear trend across 3 groups for walking 10 ft and grip strength. In Ps with chronic conditions, high EEs were 40–120% more likely to have optimal physical function.			
Van den Hornbergh et al., 1995 (60)	493 M, 503 F 65–69 yr 70–74 yr 75–79 yr 80–84 yr Com living Dutch	Quintiles: Low = lowest Med = 2, 3, 4 High = 5 Derived from total activity score from questionnaire Intensity code based on net energetic costs and time spent	Random sample 1 data collection	PA associated with living in houses without stairs. Old age and physical disability strongly related to low PA, especially for women. Lo vs Hi Active Physical disability OR = 2.8 (F), 7.1 (M)	PA associated with old age and physical disability strongly related to subjective health. OR = 7.6 (F), 6.8 (M)		
Frandin et al., 1995 (19) Evergreen Project Jyvaskyla, Finland	172 M, 131 F Part of a long study of 70-yr-olds; measured at 76 yr Com living; all citizens born in 1914 and 1910; these data from 1994–95	PA groups: 1. Hardly any 2. Sitting, walk, 3. Light exercise 4 × wk 4. Moderate exercise 1–2 hr·wk 5. Moderate exercise 3 × wk 6. Hard exercise regularly, several times a week Self-report	Cross-sectional nonparametric analyses Regression of physical function on PA levels	In males, correlations between PA and physical performance were sig and low to moderate: 66–75 r = 0.26 to 0.38 51–65 r = 0.16 to 0.26 37–50 only 1 sig r, walk speed, r = 0.22 Number and size of correlations increased during older and older decades, higher in men than women.			
Laukkanen et al., 1998 (30) 1914 1910 Evergreen Project Jyvaskyla, Finland	117 M, 228 F 75 yr 61 M, 157 F 80 yr Com living Relatively high activity 75–80 yr olds	PA groups: 1. Hardly any 2. Sitting, walk, 3. Light exercise 4 × wk 4. Moderate exercise 1–2 hr·wk 5. Moderate exercise 3 × wk 6. Hard exercise regularly, several times a week Self-report	Prospective Descriptive Gender differences ORs for disability mortality disease, 5 yr 1989–90 to 94–95	Persons more physically active at baseline were less physically disabled 5 yr later. Among 75-yr-olds, risk of 3 or more PADL limitations (OR = 2.47–3.51) or a serious disease (OR = 2.50–3.99) 5 yr later was greater in sedentary people than active people.			

AADL, Advanced Activities of Daily Living; ADL, activities of daily living; Com living, community living; EE, estimated energy expenditure; EPESE, Established Populations for Epidemiologic Studies of the Elderly (Simonsick et al., 1993); IADL, Instrumental Activities of Daily Living; LISREL, LInear Structural RELations (a computer program to develop structural equation models); MANOVA, multivariate analysis of variance; ML, myocardial infarct; NS, not significant; OR, odds ratio; P, participants; PA, physical activity; PADL, physical activities of daily living; PASE, Physical Activity Scale for the Elderly (New England Research Institutes, 1991); WHAS, Women's Health and Aging Study; sig, significant.

[a] Dose-response: physical activity levels (Evidence Category C).

TABLE 4. Aerobic/resistive exercise interventions and quality of life, nonrandomized, Evidence Category C.

References	Participants	Exercise Mode and Dose	Study Design	Physical Function	Cognitive/Engagement with Life	Health Status Disease	Well-Being
Stewart et al., 1993 (55)	111 M, 83 F Ages 50–85 yr M = 58.0 Com living	*Aerobic training*: Walk/jog *VH intensity* (73–88% HRp): G1. Class-based G2. Home-based *Moderate intensity* (60–73%): G3. Home-based 40-min sessions 3 × wk Total: 1 yr	Posttest only No control group	Higher for groups that participated in training at higher levels; >100% group >0–33% and 34–66% group; 67–100% > 0–33% group self-report of limitations in walking, climbing hills, bending, lifting		NS: Current health perceptions	NS: Well-being.
Topp and Stevenson, 1994 (59)	97 started, 66 finished; 60–81 yr Com living	*Aerobic training*: Cycle ergometer *Light intensity*: 30–40% HRR *Hard intensity*: 60–70% HRR 30-min sessions 3 × wk	Pre-post, w/o control Randomized to treatments Measures at: baseline, 4.5 mo, and 9 mo	Intensity not a factor; mean training intensity same for high and low	Intensity not a factor. Both groups improved in mental function.	Intensity not a factor. Outlook improved in rejection of the sick role and health.	Intensity not a factor. Life satisfaction within either group NS.
Emery and Blumenthal, 1990 (14)	M 50, F 51 60–83 yr Com living	*Aerobic training hard intensity*: Aerobic (N = 33) 70% HRR Yoga (N = 33) Wait-list (N = 34) Total: 32 wk	Quasi-experimental with control group, ANOVA with repeated measures: T1 pre T2 16 wk T3 16 wk T4 6 mo	*Perception* of physical change, more than other changes, was correlated to objective change; to VO_{2max}, r = 0.36, $P <$ 0.01, time on bike ergometer, r = 0.42, $P < 0.001$	*Perceived* changes in mental function higher in aerobics and yoga groups. Percent time in training range correlated with *perceived* changes in family relations r = 0.42, $P < 0.05$ and not correlated with objective measures.		After 6 mo AT group, more than other two groups *perceived* change in all 19 QL dimensions; % time in training range correlated with Mood, r = 0.53, $P < 0.01$; confidence, r = 0.36, $P < 0.05$; life satisfaction, r = 0.43, $P <$ 0.05; loneliness, r = 0.37, $P <$ 0.05.
Cowper et al., 1991 (9)	43 Ps started, 23 finished M 90% F 10% 65–80 yr Elderly veterans in Gerofit program	*Aerobic training hard intensity* (65–75% HRR) Supervised classes; 90 min 3 d·wk Total: 1 yr	Baseline and 1-yr follow-up, participation vs nonparticipation	40% of Ps ↑ in aerobic fitness, strength, METs, flexibility, DBP Decreased BMI		40% of Ps reported better overall health, (baseline SIP were low to minimal dysfunction) and Ps changed minimally by study.	↑ well-being, 30% ↑ in mental outlook, dropouts and adherents different at baseline in requiring household help and SIP (physical).
Brandon et al., 2000 (4)	10 Controls 15 M, 28 F 10 M, 32 F M = 72.3 Com living	*Moderate to Hard*: Lower limb RT 50–70% 1 RM 60 min, 3 × wk Total: 4 mo	Group × time ANOVA E = exp C = control	↓ Floor rise time ↓ Chair rise time No Δ 50-ft-walk time and time climbing up or down flight of stairs Ps in this study began stronger than Ps in other studies Only threshold strength levels necessary for mobility other than floor and chair rises. E ↑ 1 RM and 1 RM/BW Plantar = 69%; knee flexion = 39%; knee extension = 41%			
Morey et al., 1999 (35)	Recruited At-risk for functional decline Spinal flexibility + aerobic (SF+) 20 M, 44 F 71.9 ± 5.8 Aerobic (AT) 21 M, 49 F 71.9 ± 4.6	*Hard Aerobic* 40 min walking and bike, 70% HRR *SF+*: 20 min aerobic and 20 min flexibility exercises; 3 supervised and one at-home session for 3 mos followed by 6 mo home-based exercise 4 d·wk Total 9 mo	Change scores: Baseline to 3 mo, 3 to 9, Baseline to 9 mo; analyzed change scores for combined groups, and separately	SF+ (20 min aerobic) = ↑ 3.8% A (40-min aerobic) = ↑ 10.9% Except for VO_{2max}, group differences were negligible Both improved spinal flexibility; no overall changes in performance measures Significant changes ($P < 0.05$); *Impairment measures*: Axial rotation and VO_{2max} ($mL \cdot kg^{-1} \cdot min^{-1}$) SF+ ↑ from baseline, 3 mo, 9 mo A ↑ from baseline, 3 mo, 9 mo *Functional measures*: NS *Disability measure*: Physical function (0–100) SF+ A = 71.6, 79.7, 73.4 A = 76.6, 79.7, 78.7			

Δ, change, difference; ↑, increase; ↓, decrease; ANACOVA, analysis of covariance; ANOVA, analysis of variance; AT, aerobic training; BW, body weight; Com living, community living; ES, effect size; HRp, peak heart rate; HRR, heart rate reserve; IDA, interdisciplinary longitudinal project; NS, not significant; PFP, physical function performance test (Cress et al., 1996); PT, physical therapists; RG, resistance training group; SF+, spinal flexibility exercises + aerobic training; SIP, Sickness Impact Profile (Bergner et al., 1981).

strength, muscular power, muscular endurance, balance, and flexibility), and the physical tasks that are necessary for daily function (walking, chair-rising, stair climbing, bending, lifting, stooping, carrying heavy objects, running, and hand function). Many of these tasks are items of the Basic Activities of Daily Living (BADL), and Instrumental Activities of Daily Living (IADL) inventories. In this review, only the relationship of exercise outcomes and PA to the ability to function in the physical tasks of daily living is addressed.

In cross-sectional, correlational studies, exercise and self-reported PA are related to levels of physical function. Exercise is frequently reported to be a positive influence of age-related changes of physical function in these studies (57,27), although Skelton et al. (53) failed to find relationships of self-reported habitual PA to functional ability. In clinical studies where exercise outcomes are quantified, strength (35), fitness (35), and muscular power (1,18) have been related to chair-rising, stair-climbing, and walking. Indeed, leg power accounted for 86% of the variance in walking speed of elderly women according to Bassey et al. (1) (Evidence Category C).

In large sample studies, both randomized and nonrandomized, an exercise effect defined by groups differing in self-reported habitual activity is clearly present (19,45). Correlations between self-reported PA levels (ranging from "none" to "high") and physical function are many times significant and low-moderate. In one study, the number and size of the correlations were increasingly higher in older and older decades, higher in men than in women, and particularly in walking speed and stair-climbing (19). When energy expenditure was estimated from self-reports of habitual PA, a linear trend emerged across low, moderate, and high daily energy expenditure for walking 10 feet and for grip strength. In addition, those who expended larger amounts of energy daily were more likely to have optimal function in BADL and IADL (65), and those who "never walk at least one mile per week" were 1.56 times more likely to decline in function and become unable to perform ADL and IADLs (33). These relationships between PA and physical function appear to be independent of sociodemographic and baseline health status (Evidence Category C).

Whether a PA group-defined "dose-response" exists, or whether an activity level threshold is operative, is unclear. Reuben et al. (45) are strong advocates that exercise levels, as defined by self-reported physical activities, form a hierarchical scale that correlates positively in a graduated manner with progressively increasing advanced ADLs (45). However, Seeman et al. (51) reported that participation in *either* moderate or strenuous PA was associated with positive changes in balance, gait, chair-stand, and foot tap. Nevertheless, *all* studies reviewed in Evidence Category C supported some type of relationship between exercise or PA and physical function in the elderly.

Aerobic training interventions have had some positive effects on walking, but primarily for distance and not for speed (28,55,59), although they have not always been shown to affect functional limitations, functional reach, and moving from a bed to standing. Intensity level of the exercise was not a factor, and differences were most frequently seen when participants in experimental groups were regrouped *post hoc* into those who worked most in the training zone or who appeared to expend more energy and attend more classes (59). Resistance training was associated with improvements in tasks requiring strength: rising from the floor (kneeling or a chair), or climbing stairs, and not activities associated with endurance, balance, or disability (8) (Evidence Category B). Other investigators failed to observe resistive training improvements in many of the physical function tasks (35). Two of these studies were short in duration (4,53), and in others, it is likely that the participants' baseline strength was above the sensitivity level of the test so that improvements could not be observed (for details, see Buchner and De Lateur (7)) (Evidence Category C).

Exercise, physical activity, mental function, and engagement with life. The components of mental function and engagement with life within the quality of life framework have received almost no attention. Although a large body of literature exists on the topic of exercise, PA, and cognition, these studies primarily focus on information processing and executive function and do not address the issues of mental operations necessary for daily function and social interactions in the elderly. Similarly, almost no studies are available in which changes in PA are related to changes in role or social activities, such as volunteer work, community activities, participation in social groups, or in hobbies and recreational pursuits. Scant evidence is available that aerobic training was related to perceived changes in family relations (14) (Evidence Category C), and that participating in a training study resulted in the participants increasing their total activity time after the training program (39,48). However, others found no difference in social or role limitations and no perceived change in social function (38,48) (Evidence Category B).

Physical function and physical activity participation as predictors of independent living. Results from a set of population-based, cross-sectional and longitudinal studies (Evidence Category C), most of which assessed thousands of older adults over the age of 65 yr, are relatively consistent in their reports of the relationship of PA and/or physical function to independent living. Regular PA and disability are inversely related; PA predicts frailty and health-related disability (30,42,52,58,61). In these studies, persons who were more physically active at baseline were less disabled several years later. Some evidence exists that equal benefits derive from walking, gardening, and vigorous exercise (29).

Physical activity is related to physical function, and function has predicted dependence and relative risk of admission to nursing homes, particularly the functions of walking speed and the ability to participate in outdoor activities (Table 6) (15,22). Low PA levels have been strongly related to physical disability (52,60). In a group of older adults high in PA, all of the odds ratios associated with physical impairment, especially the one-half-mile walk, were <1.00,

TABLE 5. Aerobic/resistive exercise and multiple indicators of quality of life, randomized, Evidence Category B.

References	Participants	Exercise Mode and Dose	Study Design	Physical Function	Cognitive/Engagement with Life	Health Status Disease	Well-Being
Cress et al., 1999 (10)	E = 23 C = 23 M and F 76 ± 4 yr Com living Retirement community	*Aerobic training* *Hard intensity* (75–80% HRR) *Hard resistance training* (75–80% 1 RM) Lower and upper body; 60 min 3 × wk Total: 6 mo	Group × time ANACOVA	CS-PFP strength domain 14%, ES = 0.80. E group carried 14% > weight and moved 10% quicker; Es ↑ 9–33% in strength and aerobic capacity NS: 6-min walk, gait speed, functional limitations		NS: Physical health status—Sickness Impact Profile (SIP)	NS: QL (SF-36 test) Depressive symptoms
King et al., 2000 (28)	M 36, F 67 65–80 yr Com living	*Aerobic and Resistance* (A+R) *Hard intensity* (60–70% HRR). A+R: 2 classes·wk + 2 home exercise·wk 40–50 min aerobics Control: stretch and tone class + 2 × wk + 2 home exercise 40–50 min stretch/relaxation Duration: 12 mo	Baseline, 6, and 12 mo group × time ANCOVA randomized to groups	A+R HRsub reduced at 12 mo, $\dot{V}O_{2max}$ and treadmill test duration, NS A+R more improved at lift and reach; No Δ in sit to stand Control men only more flexible		Greater improvements in pain levels (M and F) at 12 mo, not at 6 mo	A+R greater *confidence* in lifting heavy objects, walking distances, and energy/fatigue scale Improvements in well-being (M and F) at 12 mo, not at 6 mo
Perrig-Chiello et al., 1998 (39)	28 18 M = 73.2 yr Com living; sample from IDA	*Resistance training* % 1 RM not given; class 1 × wk Control group Duration: 2 mo	Experimental control; Pre/post; Posttests also compared to larger IDA baseline (N = 268) 1 yr later	Significant increases in trained group: ↑ leg power at posttest and 1 yr (P = 0.02)	NS: Posttest difference in cognition Trained greater control and IDA sample on recall memory 1 yr later; both groups active in more sports than IDA sample	NS: Health ratings	NS: Well-being Control beliefs Self-efficacy Internal self-control
Peel et al., 1999 (38)	Experimental group: F 2, M 11 77.7 ± 4.4 yr Control group: F 2, M 9 75.5 ± 5.1 yr physically limited patients in outpatient clinic	*Aerobic and resistance* (A+R) Brisk walking 20 min at 60–80% HRmax; *Resistive exercise* 3 sets of 10 reps upper and lower limb 3 sessions·wk 60-min sessions Duration: 2 mo	Groups ANOVA	A+R: ↑ treadmill test performance, ↓ HR, SBP ↑ upper body strength, but hip and knee extension NS NS: A+R *and* C ↑ physical performance scores due to learning	NS: *perceived* change in social function	NS: *perceived* change in general health, vitality, or bodily pain	A+R and C *perceived* physical function (P = 0.03) and role emotion (P = 0.02 to improve (SF-36 Health Survey)
Brown et al., 2000 (6)	Exercise class: 20 M, 28 F Ages 83 ± 4 yr Home-based: 17 M, 22 F Ages 83 ± 4 Ps must score <32 on PPT Com living	*Resistance training* by low-intensity functional exercises to challenge all major muscle groups, flexibility, and balance, therabands, 1–2 lb hand-held weights; floor-exercise Duration: 3 mo	2 × 2 ANOVA groups × pre/post	Significant improvements in PPT scores; specifically in chair rises, putting on and taking off a coat, picking up a penny, and the Romberg balance test. Shoulder abductors increased in strength in exercise group (9%) but slightly decreased in home-based flexibility group (–1%). Flexibility increased in both groups. Significant changes in obstacle course performance, full-tandem Romberg test, Berg balance test, and one-limb standing. No changes in Home-based flexibility group on anything but flexibility. Significant change in preferred walking speed in exercise group.		No changes in RT (cognition) for either group	No changes in sensation in either group; Tactile acuity Proprioception
Rubenstein et al., 2000 (48)	59 M C = 58 E = 31 74 yr, Com living	*Aerobic and resistance training* (A+R) 90 min, 3 × wk 3 mo elastic bands light weights	Ps with high risk factors for falling; randomized to 2 E and C groups	E > C in gait and endurance E ↑ reps on sit-to-stand 23% compared with C, 4% No change in: Obstacle test, balance Cs fell > Es during 3 mo	↑ total activity time in A+R NS: Role limitations	A+R self-rated global health > Cs after intervention	NS: Health perceptions

TABLE 5. *Continued*

References	Participants	Exercise Mode and Dose	Study Design	Physical Function	Cognitive/Engagement with Life	Health Status Disease	Well-Being
Chandler et al., 1998 (8)	E = 50 77.5 ± 7.1 yr C = 50 77.7 ± 7.8 yr Com living Also, grouped by low and high function, based on chair-rise	*Resistance training* (RT) with therabands and light body weights 3 home sessions·wk by PTs; lower limbs Progression based on ACSM guides and theraband color coding	Two sample paired *t*-tests of group Δ scores; regression to determine Δ in strength on Δ in performance scores Separate models for: Less frail More frail	E = ↑ 9–16% strength, C = ↓ 1–3%; Δ in strength to Δ significant for mobility, gait speed, falls efficacy (R^2 = 0.76, 0.78, 2.9) Pre to post significant for strength No Δ in endurance, functional reach, static sway and MOS scores			No change in depression
Greendale et al., 2000 (21)	62 M and F M = 74 yr Com living	Wearing a weighted vest, 2 hr·d, 4 d·wk No vest (*N* = 21) 3% weight (*N* = 19) 5% weight (*N* = 22) Duration: 6.75 mo	Randomized control group × time ANOVA	NS: Walk, 8 ft, 50 ft, NS Functional reach Stair climb, chair stand, leg stand *No treatment effect* NS: Well-being Falls efficacy Energy Locus of control *No treatment effect*	NS: Social function Role-limitations	*No treatment effect*	NS:Pain *No treatment effect*
Fiatarone et al., 1994 (16)	RT = 9 M, 16 F 86.2 yr RT+ S = 9 M, 16 F 87.2 yr S = 18 M, 7 F 85.7 yr C = 14 M, 12 F 89.2 yr Dep living	*Resistance training* (RT) Knee and hip extensors 3 d·wk 80% 1 RM 45 min Duration: 2.5 mo	3 group × rep measures forward step regression to determine R among significant variables	Training improved gait velocity, stair-climbing, and increased overall physical activity; 4 Ps progressed from walker use to cane assistance			
Rooks et al., 1997 (47)	131 gender not reported 65–95 yr Com living; 12 communities Boston, MA	*Resistance training* and stair climb (weighted belt ↑ wt), 3 sets of each exercise *Walking* 3 × wk Total: 10 mo	3 groups: resistance walking control ANOVA	Knee extension strength ↑ in resistance group (RG), ↓ in other two groups. RG group improved more in most balance tests, reaction time, and pen pick-up. Both RG and walkers ↓ stair climbing time, but not controls. NS: hand strength changes.			
Skelton et al., 1995 (53)	Women only E = 20 C = 20 M = 79.5 75–93 yr Com living Healthy but relatively low PA	*Resistance training* 1 class and 2 home sessions·wk 30–40 min; 3 sets 4–8 reps rice bags and tubing Total: 12 wk	Quasiexperimental Matched for age and PA Randomized to treatments Group × time ANOVA and ANCOVA	Functional reach, rise from chair, knees, lying on floor, lifting bag, box-stepping, stair climb 6 flights Walking 118 m ↑ s in strength: Knee extension, 27%, P = 0.03 Elbow flexion, 22%, P = 0.05 Leg extension power/kg, 18%, P = 0.05 E > C in kneel rise time, change = 21%, P = 0.02 No other functional tests improved			

Δ, change, difference; A+R, aerobic and resistance training; A/R, aerobic or resistance training; C, control; CS-PFP, Continuous Scale—Physical Function Performance (Cress et al., 1996); E, Exercise, exercisers; ES, effect size; IDA, Interdisciplinary Longitudinal Project (Perrig-Chiello et al., 1998); NS, not significant; Ps, participants; PFP, Physical Function Performance test (Cress et al., 1996); PPT, Physical Performance Test (Reuben and Siu, 1990); RT, resistance-trained group; QL, quality of life; S, multinutrient supplementation; R + S, resistance training + multinutrient supplementation; SF-36, Self-perceived Physical Function Scale (Bergner et al., 1981); SIP, Sickness Impact Profile.

TABLE 6. Physical function and physical activity participation as predictors of independent living.

References	Participants	Physical Function/PA	QL Indicators	Study Design	Results
Hirvensalo et al., 2000 (25)	179 M 336 1988: 65–84 1996: 73– Com living	Mobile-active (M-A) Mobile-sedentary (M-S) Impaired-active (I-A) Impaired-sedentary (I-S)	Loss of independence: nursing home, hospital, assisted-living, receive public funded assistance Mortality	Longitudinal 8 yr Baseline 1988	OR for loss of independence Men Women M-A = 1.00 1.00 M-S = 0.91 1.17 I-A = 1.14 1.99 I-S = 5.21 2.92 PA protects mobility-impaired from further disability measured as loss of independence. Older adults with chronic diseases but higher PA levels less likely to lose mobility than sedentary counterparts. PA has great potential for preventing worsening of disability and mortality among those initially independent but mobility impaired.
Falconer et al., 1991 (15) Com living Homebound Institutional	702 M and F 74.6 ± 8.8 77.9 ± 8.0 84.5 ± 5.8	Hand function Williams Board Williams Test, Jebsen Test Grip strength GERI-AIMS dexterity and functional scales	Independent living	Descriptive Three-group comparison ANOVA Discriminant analysis of predictors for living status	After demographics, which correctly identified the living status of 68% of Ps, the following increased the prediction to: Williams Board—74% Williams Test—74% GERI-AIMS functional scores—80% Results weakened by significant age differences across groups.
Guralnik et al., 1994 (22) EPESE	5174, 71+ yr Com living or nursing home	Physical performance summary score: tandem, semitandem, side-by-side balance; walking speed, 8 ft rise from a chair Self-report ADLs; lower extremity function	Nursing home status Mortality per person year of 18-mo follow-up	Population-based longitudinal Baseline data 1981–83; These data 1988–89, 18 mo	Increasingly better performance on timed walk, chair stand, and balance associated with stepwise decrease in % reporting disability. Summary performance scale; strong association between performance measures and disability RR of Nursing Home Admission (men, women) Age: 1.8, 1.9 ADL 1.1, 1.2 Walk ½ mile 1.2, 1.4 Stair climb 1.9, 1.2 Performance 2.7, 2.2
LaCroix et al., 1993 (29) EPESE	3046 M 3935 F 2 age groups: 65–74 yr ≥75 Com living	Self-report: high PA vs low PA; walks, gardening, vigorous exercise Based on a 1–3 scale that included frequency	Mobility Maintained Lost mobility Died w/o losing mobility	Population-based longitudinal Baseline data 1981–83; These data 1987–88 4 yr	For men and women, regular PA associated with 40% decreased risk of losing mobility (RR = 0.4–0.7). PA benefits independent of health status (chronic disease). Equal benefits for walking, gardening, vigorous exercise.
Rantanen et al., 1999 (43) Honolulu Heart Program	3218 M 45–68 yr Com living	Engaged in PA and produced sweat 3 groups, based on baseline grip, strength tertiles	Disability index: Last yr Last 2 yr Chronic conditions Functional limitations: Walking speed 10 ft Rise from chair	Longitudinal Descriptive 26 yr ORs for disability	Baseline grip strength did not predict survival; clear gradient of increasing risk for all functional limitations and disability outcomes based on grip strength tertiles at baseline. Grip strength may be a marker of PA
Vita et al., 1998 (61)	1341 M, 400 F M = 75 yr Baseline U Penn 1939–1940	Ps categorized as low, moderate, or high risk for disability at baseline (1962 and 1986) Risk factors: smoking, BMI, exercise, no. min of vigorous exercise per week 0, 1–119, 120–239, >240	Cumulative disability from 1986–1994 baseline data 1962	Longitudinal Descriptive 8 yr	Ps with high risks in 1962 or 1986 had twice the cumulative disability of those with low risk (1.02 vs 0.49, $P < 0.001$). Results consistent among survivors, those who died, men and women, and for both the last year and the last 2 yr of observations.
Cunningham et al., 1993 (12) Com living	20 M, 77.4 ± 8 44 F, 75 ± 5.0 20 M, 82.3 ± 6.3 41 F, 79.8 + 6.8 Nursing home (Dependent)	Activity levels household chores; leisure/work; outdoor act	Independence (incapacity index) flexibility; CV fitness, strength Walk speed, 20 m	Nonrandomized Cross-sectional Two-group comparison	40% of variance in Incapacity Index (independence) was associated with participation in outdoor activities, greater shoulder flexibility, and faster normal walking speed. Most significant predictor of independence was choice of walking speed (30.4% of variance).
Fries et al., 1994 (17)	458 M runners 76 F runners 114 M nonrunners 133 F nonrunners healthy, Com living	Runners club and community controls in intent-to-treat analysis (451 vs 330) Regrouped into ever-runners and never-runners	Disability 8 yr from baseline. by Stanford Health Assessment Questionnaire	8-yr prospective longitudinal, with annual assessment	Male runners accrued disability at rates 40% lower than controls; female runners 89% lower; with demographic variables and comorbidity factors accounted for, disability still 64% lower in runners. Results similar in both analyses: intent-to-treat, and as-treated (ever-runners vs never-runners).
Schroeder et al., 1998 (50)	Nursing home (23) Asst Living (23) Com living (23) Volunteers	PA level: PAQE, PPT, Up and Go, 1 RM knee extension and double leg press; modified sit-and-reach	Satisfaction with Life Scale Group differences in living status	One-way ANOVA for living status differences	NS: Satisfaction-with-life scores across living status PA: Com living = Asst living ≫ Nursing home PPT: Com Living > Asst living > Nursing home Up-and-go: Com living > Asst living > Nursing home Strength: Com living > Asst living > Nursing home Flexibility: Com living > Asst living = Nursing home Decline in physical performance and PA are related to lower levels of strength, balance and flexibility; all Related to loss of independence.

ADL, activities of daily living; Asst Living, assisted living; BMI, body mass index; Com living, community living; EPESE, Established Populations for Epidemiologic Studies of the Elderly (Cornoni-Huntley et al., 1986); Ind, independent; Dep, dependent; OR, odds ratio: Ps, participants; PA, physical activity; PAQE, Physical Activity Questionnaire for the Elderly (Voorips et al., 1993); PPT, Physical Performance Test (Reuben and Siu, 1990); RG, resistance trained group: RR, relative risk.

and a graded response was observed between PA level and impairment. In a smaller, more descriptive study of 27 institutionalized elderly over a 2-yr period, poor performance in grip strength, ambulation, manual ability, and poor cognitive function predicted the transfer to a skilled nursing care facility (60). In addition, regular PA appears to protect

the mobility-impaired from further disability (25,29,30,45). Thus, even in individuals with chronic disease, those who expend more energy in physical activities on a systematic basis are more likely to have optimal physical function (65).

A potential risk factor that has been neglected in most programs designed to postpone disability and dependence is that of hand function. From grip strength tertiles at baseline, 26 yr later a gradient of increasing risk emerged for all functional limitations and disability outcomes (42). Hand function on coordination tests increased the ability to differentiate dependent living status from 68% (which was determined on the basis of demographics), to 74% (15). Grip strength may be a marker of habitual PA.

RECOMMENDATIONS

1. Ensure that if possible, every participant in an exercise intervention group actually experiences a treatment effect.
2. Report effect sizes in intervention studies. Results of experimental studies cannot be compared very well without effect sizes.
3. In intervention studies, match the participants' ability level and the training modality to the task requirements.
4. Establish norms for assessment of walking speed at a standardized distance, so that factors influencing walking speed can be compared across studies.
5. Develop a standard method of quantifying PA that is feasible to use with moderately large and disparate samples, and encourage its use by all researchers.

FUTURE RESEARCH PRIORITIES

1. Determine the effectiveness of introducing PA at various ages in life in preventing, delaying, and/or reversing functional dependence. The question is not whether a lifetime of PA can postpone disability, but whether the benefits are diminished with advancing age, and if so, how much.
2. Study the relationship of muscular strength and power to physical function. If this relationship is curvilinear rather than linear, characterize that relationship and determine threshold values, below which function is greatly impaired.
3. Determine whether the relationships between PA levels and physical function differs for men and women, and if so, in what ways. Gender factors associated with changes in physical function may be substantial (19,57) and should be clarified.

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Chair summary and contents

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Defining the dose-response relationship between a behavior and associated risks and benefits to human health is never simple. It is, surely, particularly complex for physical activity, which may be practiced in so many forms and to different degrees. Drawing an analogy with the requirements for getting a prescribed medication approved by the Food and Drug Administration in the United States, Haskell identified in 1995 key issues in the assessment of exercise "dose" and of responses in terms of health-related outcomes (2). He underlined just how much remains to be done in the search for science-based recommendations for evidence-based health care delivery and disease prevention. Achieving this goal will require the integration of different types of evidence (observational, experimental) from all sorts of disciplines (e.g., physiology, cell-biology, genetics). Furthermore, science and medicine must interact so that health outcomes are assessed and reported in terms of their clinical importance. The balance between benefits and risks of exercise is fundamental to public health policy and the data presented on the increase in exercise-related injuries among over 55-yr-olds (and associated costs) serve as a timely reminder of the need for objective assessment of the risks of exercise.

Thune and Furberg's extensive review of observational studies suggests that both leisure-time and occupational physical activity are associated with a lower risk of total cancers, with a dose-response suggested for both sexes, but varying by specific cancer sites. The relation between physical activity and reduced colon cancer risk displays a strong dose-response relation, but there was no relation with rectal cancer. There is a strong gradient effect from physical activity on reduced breast cancer risk among pre-, para-, and postmenopausal women, together with a gradient effect of exercise on endometrial cancer. Suggestive evidence supports a gradient protective effect of physical activity against lung cancer, but questions of residual confounding remain. Mixed dose-response results leave unanswered questions about relations between physical activity and prostate cancer, and between activity and testicular cancer (3).

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Appropriately, Vuori, in addressing the complex relations of physical activity with musculoskeletal functioning, considered possible negative as well as positive effects. He presented a biologically plausible rationale for a primary preventive role in relation to each of three conditions, i.e., low back pain, osteoarthritis, and osteoporosis. However, research into physical activity and low back pain has been hampered by the lack of understanding of the underlying pathology and its relations with pain and perception of this. The proposition that leisure time physical activity may have a primary preventive effect was suggested by findings from two RCTs but has been insufficiently tested. Specific types and intensities of activity, for example, heavy occupational work, have been found to increase the risk of low back pain but no other information on dose-response issues was available. By contrast, a large body of evidence was found showing that resuming normal physical activity opposes deconditioning and lessens disability after an acute episode of back pain.

Vuori explained the practical problems of investigating dose-response issues in relation to osteoarthritis. He found no evidence for a primary preventive effect of physical activity, although habitual use of joints within normal limits causes physiologically beneficial effects and an indirect benefit may be postulated through avoidance of overweight. Observational studies of athletes and of people involved in heavy occupational work suggested a hierarchical relationship with risk of osteoarthritis that increases with degree of loading, but predisposing factors, such as deformities and malalignments as well as clinical and subclinical injuries to joints, are likely to be strong contributory factors to development of osteoarthritis.

Evidence presented for beneficial effects of physical activity on bone mineral density (BMD)—and, by inference, the risk of developing osteoporosis—was extensive and rather consistent. High-intensity loading causes a local osteogenic response at the loaded site, with responsiveness dependent on the hormonal milieu. It is uncertain whether light- to moderate-intensity exercise can influence BMD in young and middle-aged, habitually active subjects.

Dose-response issues are clearly difficult to address in all these areas, not least because of uncertainties concerning the parameters that need to be measured. These seem best described for BMD and least well described for low back pain. Basic research is required to uncover the

specific roles of load magnitude, repetition, and rate of application as determinants of beneficial and/or detrimental effects in relation to each outcome considered. The potential negative effects of some exercise regimens are obvious and so the balance between risks and benefits is an important public health issue. When formulating recommendations for physical activity, it will be necessary to take a holistic view, not least because those activities most likely to increase the risk of osteoarthritis are (theoretically at least) those most likely to cause momentary microscopic deformation of bone and provoke an optimal osteogenic response. Clarification of dose-response issues in these areas may help us to understand factors dictating the risk/benefit balance at different stages of life.

Dunn et al. presented a summary of evidence on dose-response issues for effects of physical activity on depression and anxiety. They restricted their review to individuals diagnosed with these problems and to specified clinical outcomes. The picture that emerged was clear. On the basis of cross-sectional and prospective studies, physical activity reduces symptoms of depression and anxiety. Only the Harvard Alumni study has explored the dose-response relationship, finding a gradient of response according to total energy expenditure. Findings from intervention studies were rather consistent, and nearly half found a clinically worthwhile response ($\geq$50% reduction in symptoms). In this category, no studies examined the effect of varying the different components of exercise. Dunn et al. defined research needs clearly and had the foresight to suggest that, because aerobic and resistance exercise both reduce anxiety and depression, research into possible mechanisms might take as a starting point consideration of what relevant effects might be common to these different modes of exercise.

Spirduso and Cronin examined dose-response effects on quality of life and independent living in older adults. Despite clear evidence from correlational and prospective studies that measures of physical function or physical activity in older adults are related to feelings of well-being, findings from intervention trials are inconsistent. As pointed out, this may relate to the failure of some investigators to match the training regimen to participants' physical capabilities. Once again, little comment could be made on dose-response relationships. One of the major problems was identified as the difficulty in defining valid measures of quality of life. This is one area where, intuitively, physical activity has much to offer—in terms of physical function (linked to dependency), sense of well-being, and risk of depression. The capability of muscle to adapt to increased activity persists into the latest decades of life (1) and so problems associated with chronic conditions—from osteoarthritis, to diabetic foot—may be limiting factors. With expenditure on health and personal care costs for older adults burgeoning, research in this area would seem to be an essential rather than a luxury.

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Health effects resulting from exercise versus those from body fat loss

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ABSTRACT

WILLIAMS, P. T. Health effects resulting from exercise versus those from body fat loss. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S611–S621. **Objective:** The purpose of this review was to assess whether body weight confounds the relationships between physical activity and its health benefits. **Methods:** The review includes 80 reports from population-based studies (Evidence Category C) of physical activity or fitness and cardiovascular disease (CVD) or coronary heart disease (CHD). **Results:** Eleven of 64 reports on activity found no relationship between physical activity and disease. Of the remaining 53 reports, 11 did not address the possible confounding effects of body weight, nine cited reasons that weight differences should not explain their observed associations, and 33 statistically adjusted for weight (as required). Only three of these changed their associations from significant to nonsignificant when adjusted. Ten of 16 reports on cardiorespiratory fitness and CHD or CVD used statistical adjustment, and none of these changed their findings to nonsignificant. Population studies show that vigorously active individuals also have higher high-density lipoprotein (HDL)-cholesterol concentration, a major risk factor for CHD and CVD, than sedentary individuals when statistically adjusted for weight. In contrast, intervention studies, which relate dynamic changes in weight and HDL, suggest that adjustment for weight loss largely eliminates the increase in HDL-cholesterol in sedentary men who begin exercising vigorously. Adjusting the cross-sectional HDL-cholesterol differences for the dynamic effects of weight loss eliminates most of the HDL-cholesterol difference between active and sedentary men. **Conclusion:** Population studies show that the lower incidence of CHD and CVD and higher HDL of fit, active individuals are not because of lean, healthy individuals choosing to be active (i.e., self-selection bias). Nevertheless, metabolic processed associated weight loss may be primarily responsible for the HDL differences between active and sedentary men, and possibly also their differences in CHD and CVD. **Key Words:** CARDIORESPIRATORY FITNESS, PHYSICAL ACTIVITY, CHD RISK, CARDIOVASCULAR DISEASE, PUBLIC HEALTH RECOMMENDATIONS, DOSE-RESPONSE, EXERCISE, EPIDEMIOLOGY, RELATIVE RISK, HDL-CHOLESTEROL, TRIGLYCERIDES, LIPOPROTEINS

The effectiveness of physical activity to reduce obesity and improve dyslipoproteinemias, insulin action and glucose tolerance, hypertension, and thrombotic profiles has been recently reviewed (21,42,82,110). This article focuses on the statistical treatment of adiposity in population studies of physical activity and health outcomes.

Physical inactivity and obesity are associated with many of the same health outcomes, including higher total mortality (97,120), cardiovascular disease (CVD) and coronary heart disease (CHD) morbidity and mortality (79,120), stroke (120,122), colon cancer (79,120), type 2 diabetes and insulin resistance (79,120), hypertension (79,120), low plasma high-density lipoprotein (HDL)-cholesterol and elevated plasma triglyceride concentrations (79,120), and preponderance of small, dense low-density lipoprotein (LDL) particles (79,137). An inverse relationship between physical activity and adiposity is evident for vigorous leisure-time activity (43,120) and is frequently observed for total activity (57,84) or leisure-time activities of mixed intensities (the association with occupational activity is less consistent) (34,86,89). Because physical activity has been proven to produce losses of both total weight and body fat (113,139,140), body fat potentially confounds the relationships between physical activity and its health outcomes.

Confounding effects (such as body weight) are traditionally eliminated by including the variable as a covariate in the statistical data analysis. In this review, it is shown that traditional statistical adjustment for body weight has little effect on the relationships of physical activity to CVD, CHD, or plasma lipoprotein levels in population studies. This is in contrast to intervention studies that suggest that the metabolic processes associated with adiposity are pivotal to the high HDL-cholesterol in runners. The discrepancy arises because the traditional approach assumes that the confounding effects of leanness are attributable to the static process of self-selection rather than the dynamic process of weight loss.

POPULATION STUDIES OF CVD AND CHD

Tables 1 and 2 summarize the treatment of weight in population studies relating physical activity and cardiorespiratory fitness to CHD and CVD. They include articles cited in Tables 4.1 and 4.2 of the Surgeon General's report (120), 13 additional articles cited in a recent meta-analysis of the dose-response relationship between CVD and physical

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TABLE 1. Population-based studies of the association of physical activity with CVD or CHD.

Study	Adjustment for Adiposity
Canadian Health Survey 7-yr follow-up study in men and women (2)	No dose-response relationship between CVD and leisure-time physical activity. Relative risks adjusted for BMI, sex, age, and smoking (2).
Zutphen Elderly Study 10-yr follow-up of 802 middle-aged Dutch men (5)	Significant linear trend for reduced risk of CVD mortality with increasing leisure-time physical activity. Adjustment for BMI did not affect the strength of the association. BMI was not different across physical activity tertiles (5).
Israeli 15-yr follow-up of 5288 men and 5229 women living in collective settlements (10)	The risk of primary myocardial infarction was 60% less in nonsedentary than in sedentary male workers. Nonsedentary workers leaner, but no adjustment for adiposity (10).
Evans County 7.25-yr follow-up of white male farmers and nonfarmers (11)	Farmers had 51% lower CHD incidence than nonfarmers, and since they were heavier for their height than nonfarmers, leanness is unlikely to explain the farmers' lower risk (11).
German 11-yr follow-up of 1904 vegetarians (12)	Compared to low activity vegetarians, more active vegetarians had fatal CVD risk that was 50% lower. BMI unrelated to CVD risk and not used as covariate (12).
British 8.5-yr follow-up of 3591 male civil servants (13)	Men who exercised vigorously during leisure time had significantly fewer CHD deaths. No adjustment for adiposity (13).
Honolulu Heart Program 12-yr follow-up of 7644 Japanese-American men (15)	Men in the upper tertile of total activity (occupational plus leisure-time) had significantly lower CHD risk than bottom tertile, adjustment for BMI had little effect on risk reduction (15).
Israeli Ischemic Heart Disease Study 21-yr follow-up of 8463 men (16)	Leisure-time physical activity associated with a 21% reduction in CHD mortality when adjusted for potentially confounding effects (Quetelet index not selected as a significant covariate) (16).
Atherosclerosis Risk in Communities Study 4- to 7-yr follow-up of 6188 men and 7852 women (23)	A 1-SD increase in the leisure-time physical activity index produced a statistically significant 22% reduction in the age, race, and center adjusted relative risk for CHD, which became nonsignificant when adjusted for regional adiposity and other potential confounding effects (23).
Puerto Rico Heart Health Program 8.25-yr follow-up of 5802 urban and 2419 rural men (25)	Inverse dose-response relationship between CHD incidence and physical activity index (occupational plus leisure-time) when adjusted for BMI in rural ($P = 0.04$) and urban samples ($P = 0.02$) (25).
Finnish 10.8-yr follow-up of 1072 men (26)	Men who expended at least 2100 kcal · wk^{-1} had 72% reduction in CVD mortality compared with men expending under 800 kcal · wk^{-1}. BMI not found to confound relationship (26).
Finnish 10-yr follow-up of 842 men and 953 women in three northern municipalities (27)	In men, the CHD risk reduction for high vs low energy expenditure was significant both before (relative risk = 0.51) and after adjustment for BMI (relative risk = 0.52). High vs low energy expenditure unrelated to CHD risk in women, regardless of whether the data were adjusted (27).
Copenhagen Male Study 17-yr follow-up of 4859 men (31)	Least active men have 70% increased risk of ischemic heart disease as those who are more active. No adjustment for adiposity (31).
Primary Prevention Study 11.8-yr follow-up of 7395 men in Göteborg, Sweden (34)	No dose-response relationship with leisure-time physical activity. BMI not used among covariates (unclear if excluded for nonsignificance or other reason) (34).
Male postal workers ($N = 1664$) employed between 1906 and 1940 and followed through December 1961 (35)	64% lower risk of fatal CHD in carriers than clerks. Only 0.5-lb difference between carriers and clerks, thus difference in adiposity unlikely to explain risk reduction (35).
Framingham Study 14-yr follow-up of 1909 men and 2311 women (36)	Significant (one-sided) inverse association with ischemic heart disease mortality in men. No adjustment for adiposity (36).
Framingham Study 24-yr follow-up of 1166 men (37)	Inverse associations of fatal and total CHD and CVD with total physical activity index (occupational plus leisure-time) significant both before and after adjustment for relative weight (37).
Alameda County Study 28-yr follow-up of 6131 adults (38)	A one-interquartile-range difference in the leisure-time physical activity score was associated with significant reduction in the relative risk for CVD before (relative risk = 0.82) and after (relative risk = 0.85) adjustment for BMI and other covariates (38).
Finnish 19-yr follow-up of 8177 twins (39)	Compared with sedentary men, the age-adjusted CHD risk was reduced by 23% for occasional exercisers and 48% for conditioning exercisers ($P = 0.0001$ for trend). The corresponding values when adjusted for BMI, smoking, hypertension, and diabetes were 16% and 32% (39).
Postmenopausal Iowa women ($N = 32,763$) who were followed for 4 yr (44)	When adjusted for current BMI, BMI at age 18, and other covariates, the relative risk for CVD mortality decreased significantly as physical activity increased (relative risk from lowest to highest activity: 1.0, 0.86, 0.55; $P = 0.002$) (44).
HMO members ($N = 615$ men and 1030 women) ≥ 65 yr old followed for 4.2 yr (45)	Adjustment for BMI only slightly diminished the risk reduction associated with walking >4 hr compared with under 1 hr (45).
Kuopio Ischemic Heart Disease Risk Factor Study 4.9-yr follow-up of 1166 men (46)	Adjustment for BMI had minor impact on the relative risk of myocardial infarction in the highest vs lowest third of physical activity (relative risk went from 0.31 to 0.34, both significant) (46).
Gothenburg Study 12-yr follow-up of 1424 women (47)	Incidence of myocardial infarction greater in women reporting low leisure-time physical activity than in other women. No adjustment for adiposity (47).
Multiple Risk Factor Intervention Trial 7-yr follow-up of 12,138 men (51)	Significantly lower risk for lowest vs second and third tertiles of leisure-time physical activity. BMI not used for adjustment; however, mean BMI identical across activity tertiles (51).
Multiple Risk Factor Intervention Trial 10.5-yr follow-up of 12,138 middle-aged men (52)	Compared with the lowest tertile of physical activity, the second tertile had 22% and 27% lower CVD and CHD mortality rates ($P < 0.05$). Corresponding reductions in the third tertile (21% and 16%, respectively) not significantly different from first tertile. Mean BMI identical across tertiles of leisure-time physical activity; not used as covariate in proportional hazards models (52).
Multiple Risk Factor Intervention Trial 16-yr follow-up of 12,138 middle-aged men (53)	Adjustment for BMI and other potential covariates slightly diminished the reduction in CHD risk associated with increased levels of leisure time physical activity (age-adjusted risk ratios went from 1.0, 0.71, 0.75, 0.69 to 1.0, 0.75, 0.81, 0.75) for the 1st, 2nd–4th, 5th–7th, and 8th–10th deciles, respectively; however, all but the 5th–7th remained significant after adjustment for BMI and other covariates (53).
Adventist Mortality Study 26-yr follow-up of 9484 men (57)	CVD risk greater in men reporting no or slight exercise during work or play compared with more active men, which persists when adjusted for BMI and other covariates (57).
Gothenburg Study 20-yr follow-up of 1405 women (58)	No significant reduction for risk of fatal myocardial infarction (age-adjusted relative risk 0.41 changed to 0.36 with additional adjustments for waist/hip ratio and other covariates) (58).
Finnish 8.9-yr follow-up of 8869 men and 9.2-yr follow-up of 10,105 women (59)	Physical inactivity (<2–3 times · mo^{-1}) associated with significantly higher cardiovascular mortality in women ($P < 0.01$) but not men ($P = 0.28$) when adjusted for BMI and other covariates (59).
Nurse's Health Study 7.7-yr follow-up of 72,488 women (60)	The trend for a lower risk for CHD going from the least to most physical active quintiles (1.0, 0.77, 0.65, 0.54, 0.46; $P < 0.001$ for trend) was only slightly weakened by adjustment for BMI (1, 0.88, 0.81, 0.74, 0.61; $P = 0.002$) (60).
Italian 5-yr follow-up of 99,029 male railroad employees (63)	Men who expended > 3000 kcal · d^{-1} at work had significantly less risk of fatal myocardial infarction than men with less strenuous jobs ($P < 0.001$). No adjustment for adiposity (63).
German Cardiovascular Prevention Study involving 6658 and 7993 person-years of experience for males and females, respectively (64)	When adjusted for BMI, men who had engaged in high activity had lower relative risk for CVD than those who did not (64).

TABLE 1. *Continued*

Study	Adjustment for Adiposity
Male drivers and conductors of London Transport Executive (65)	Risk of first coronary episode 30% lower in conductors than drivers. No adjustment for adiposity (65).
London 5-yr follow-up of 667 bus drivers and conductors (67)	Conductors have 47% lower risk for ischemic heart disease than drivers. Skinfold thickness does not appear to explain the association (67).
British 8.5-yr-follow-up of 17,944 male civil servants (68)	Compared with men who reported no vigorous activity during leisure time, those who exercised vigorously had 55% lower incidence of coronary heart disease. When stratified for weight, the risks were 0.46 for BMI $\leq$ 23; 0.43 for 23 $<$ BMI $\leq$ 25; and 0.64 for 25 $<$ BMI $\leq$ 28 (68).
British 9.34-yr follow-up of 9376 male civil servants (69)	CHD inversely related to frequency of vigorous aerobic activity, significant both before ($P < 0.005$) and after ($P < 0.025$) adjustment for BMI and other covariates (69).
Longshoremen ($N = 6351$) followed for 22 yr (72)	Risk of fatal heart attack 44% lower in high-energy compared with the low-energy occupational category. Significance persists when adjusted for BMI and other risk factors (72).
Longshoremen ($N = 3686$) followed for 22 yr (73)	Risk of fatal heart attack 37% lower in high-energy compared with the low-energy occupational category. BMI only weakly related to risk (73).
Harvard Alumni Study 6.9-yr follow-up 16,936 men (74)	The RR for heart attack was 0.65 for men who expended $>$ 2000 kcal $\cdot$ wk^{-1} at walking, stair climbing, and sports play compared with other men. Significant when adjusted for BMI. The risk reduction was similar for men with higher (relative risk = 0.75) and lower BMI (relative risk = 0.60) (74).
Harvard Alumni Study 12.62-yr follow-up of 16,936 men (75)	Inverse dose-response relationship between CHD and physical activity when stratified by BMI ($P < 0.001$). Increased risk associated with $<$2000 kcal $\cdot$ wk^{-1} when BMI used as a covariate ($P < 0.001$) (75).
Harvard Alumni Study 8.8-yr follow-up of 10,269 men (76)	Men who climbed fewer than 20 flights of stairs per week and did not engage in moderately vigorous activity were at 56% and 51% greater risk for fatal CHD than men who climbed more stairs or engaged in moderately vigorous activity when adjusted for age, smoking, BMI $>$ 26, and family history (76).
Finnish 20-yr follow-up of 636 men (78)	Men who worked hard in their occupation and also walked, cycled, or skied cross-country had lower CHD mortality than less active men (R.R. = 0.71, $P = 0.11$), which was weakened slightly when adjusted for BMI and other risk factors (R.R. = 0.77, $P = 0.13$) (78).
Iowa study of occupation listed on 61,922 death certificates (80)	Significantly lower standardized mortality ratios for ischemic heart disease in farmers than all Iowa men. Probably not because of adiposity, since farmers heavier than townsmen (80).
Iowa women drivers (32,898) followed for 4.3 yr (81)	Leisure-time physical activity unrelated to age-adjusted risk of fatal myocardial infarction (81).
Honolulu Heart Program 23-yr follow-up of 7074 Japanese men (84)	Adjustment for BMI increased the relative risk of CHD in the highest tertile of physical activity from 0.83 (95% confidence interval; 0.70–0.99) to 0.89 (0.75–1.06) (84).
Göteborg Primary Prevention Study 20-yr follow-up of 7142 men (85)	Adjustment for BMI and other potential confounders reduced the relative risk of CHD mortality in the two most active groups from 0.55 to 0.72 when compared with the sedentary group, but did not eliminate the significance of the risk reduction (85).
Federal employee 3-yr follow-up study of 1741 men (86)	Total activity unrelated to CHD when adjusted for other risk factors (not including BMI) (86).
Finnish study of approximately 7-yr follow-up 3978 men and 3688 women (89)	Adjustment for BMI and other risk factors eliminated the significant associations between age-adjustment leisure-time physical activity and acute myocardial infarction in both men and women, and the significant association between leisure-time physical activity and fatal ischemic heart disease in men (89).
Finnish 6-yr follow-up of 15,088 men and women (90)	Age-adjusted leisure-time physical activity inversely related to fatal ischemic heart disease, but not when adjusted for various covariates (BMI not included). Excess risk of fatal ischemic heart disease in men with low leisure-time physical activity was marginally greater in obese men than in nonobese men (90).
Northern and Central Italian 25-yr follow-up study of 1712 men (96)	The relative risk for CHD mortality was 0.81 for strenuous workers compared with sedentary workers ($P < 0.01$). No adjustment for adiposity (96).
University of Pennsylvania 22.4-yr follow-up of 1564 female alumnae (99)	The age-adjusted relative risks for CVD were 1.0, 0.99 and 0.86 for $<$500, 500–999, and $\geq$1000 kcal $\cdot$ wk^{-1} from stairs climbed, blocks walked, and sports played ($P = 0.37$ for trend). When adjusted for BMI and other covariates, the corresponding values were 1.0, 0.99, and 0.86 ($P = 0.45$) (99).
Harvard Alumni Study 13.3-yr follow-up of 12,516 men (100)	Compared with men who expended under 2100 kJ $\cdot$ wk^{-1} at climbing steps, blocks walked, and sports, the age-adjusted risks for CHD was reduced by 15%, 25%, 27%, and 27% ($P < 0.001$ for trend) for 2100–4199, 4200–8399, and 8400–1599 kJ $\cdot$ wk^{-1}. The corresponding risk reductions were 10%, 19%, 20%, and 19% when further adjusted for BMI and other covariates (100).
British Regional Heart Study 8-yr follow-up of 5714 men (101)	When adjusted for BMI, there was a strong inverse association between heart attacks and physical activity (101).
Framingham Study 16-yr follow-up of 1404 women (103)	No dose-response relationship with physical activity index (occupational plus leisure-time). Metropolitan ideal weight used as covariate in proportional hazards regression mode (103).
U.S. Railroad Study 17- to 20-yr follow-up of 2562 men (105)	Significantly lower CHD risk associated with any light to moderate activity or any intense leisure-time physical activity. BMI not used as covariate because it showed no relationship to CHD mortality (105).
Belgian Physical Fitness Study 5-yr follow-up of 2106 men (106)	Both occupational and leisure-time physical activity unrelated to ischemic heart disease. No adjustment for adiposity (106).
Nurses Health Study 14-yr follow-up of 84,129 women (109)	The age-related relative risks for CVD were 1.0, 0.87, 0.84, 0.74, and 0.71 for $<$1, 1–2.2, 2.3–3.5, 3.6–5.5 and $>$5.5 hr $\cdot$ wk^{-1} of moderate to vigorous activity. Exercising $>$5.5 hr significantly lower risk compared with $<$1. BMI significantly related to CVD risk but not selected as covariate (109).

activity (125), and additional articles identified through electronic literature search. Rather than directly measuring the body fat, an index of weight adjusted for height was used in these studies.

Eleven of the 64 articles listed in Table 1 found no relationship between physical activity and disease, and 53 found at least some significant relationship. Among the latter, 11 reported no adjustment for weight, nine cited

TABLE 1. *Continued*

Study	Adjustment for Adiposity
Norwegian 14.6-yr follow-up study of 25,058 middle-aged men and 24,535 women (111)	Unadjusted relative risk for coronary deaths unrelated to leisure-time physical activity (111).
Two-yr follow-up of 191,609 male railroad employees (112)	Death rate for arteriosclerotic heart disease in the section men (the most active occupational group) was 51% lower than in clerks and 28% lower than switchmen. No adjustment for adiposity (112).
Scottish Heart Health Cohort Study of 5754 men and 5875 women who were followed for 7.6 yr (119)	Hazard ratio for CHD increased significantly with increasing levels of inactivity at work in men and women and during leisure in men. No adjustment for weight (119).
British Regional Heart Study 3-yr follow-up of 4311 men (121)	CVD mortality lower in moderately active (risk ratio = 0.26) and vigorously active (risk ratio = 0.43) men compared with inactive men. When adjusted for BMI and other covariates, risk ratios continue to be significantly less than 1 for moderate but not vigorous activity (121).
Canadian Survey Fitness cohort 7-yr follow-up of 6620 women (123)	Physical activity significantly associated with CVD, no adjustment for BMI reported (123).
Gothenburg 8-yr follow-up study of 775 men born in 1913, and Primary Prevention Trial 2.5- to 5.5-yr follow-up of 8125 men in Göteborg (124)	No significant relationships between leisure-time physical activity and myocardial infarctions when adjusted for covariates (adiposity not included among covariates) (124).
Honolulu Heart Program 10-yr follow-up of 7705 Japanese-American men (141)	Men who developed CHD were significantly less physically active and heavier than those without disease at baseline. Total physical activity inversely related to CHD risk when adjusted for BMI and other potential confounders (141).

reasons that weight differences should not explain the observed association (the active group is not leaner than the sedentary group, weight is unrelated to CHD or CVD, or the association persists when the observations are stratified by weight), and 33 present findings adjusted for weight (if necessary, i.e., also included are those studies that did not select weight as a required covariate in a stepwise selection process). Only three of these 33 articles found that adjustment for weight changed the associations between physical activity and disease from significant to nonsignificant.

The 16 reports of cardiorespiratory fitness all reported at least some significant association of fitness with CHD or CVD (Table 2). Five of these did not adjust for weight and one argued that weight adjustment was unnecessary because weight was unrelated to fitness. None of the remaining 10 reports changed the significance of their findings when they adjusted for body weight.

These studies suggest that statistical adjustments for body weight had little impact on the associations of physical activity or cardiorespiratory fitness with CVD or CHD. We cannot exclude the possibility that the published articles represent a biased sample of studies. It is possible that the articles that adjusted away the association between physical activity and disease were less likely to be submitted or accepted for publication, or that adjusted results were not reported when they eliminated significant findings. However, the articles that omitted weight adjustment tended to have earlier publication dates and to have studied occupations. It is likely that multivariate statistics were less accessible for early publications and that occupational studies may have lacked data on body weight.

POPULATION STUDIES OF PLASMA HDL AND OTHER LIPOPROTEINS

Although the mechanisms for protective effects of exercise are not well understood, it is probable that the creation of more favorable plasma lipoprotein profiles are partly involved. Low CHD risk is associated with higher concentration of HDLs, particularly the HDL2b subfraction, and lower concentrations of LDLs, triglycerides, and small dense LDL particles (3,33). The reduction in risk may accrue from both the atherogenic and thrombotic properties of these lipoproteins (87).

Numerous population studies show higher HDL-cholesterol concentrations in vigorously active men and women compared with their sedentary counterparts (1,3,14,28–30,50,55,61,62,70,71,83,93–95,108,114–116, 118,133,138). Most purport that the relationship between physical activity and plasma HDL concentrations is not attributable to body fat because: 1) the difference persists when adjusted for weight by ANCOVA (29,30,133); 2) long-distance runners have significantly higher HDL-cholesterol levels than naturally lean, sedentary men (55,71,95); and 3) HDL-cholesterol and adiposity levels are only weakly correlated within the sample of runners or sedentary men (1,62,138). Two large studies have recently documented the relationship of HDL-cholesterol to exercise amount (43,130). HDL-cholesterol was associated with a 0.005 $mmol \cdot L^{-1}$ increase per kilometer run in 2906 students and employees of the National Defense University (43). Physician-supplied medical records for men who participated in the National Runners' Health Study showed that each 16-km incremental increase in weekly running distance between 0 and 80 $km \cdot wk^{-1}$ was associated with a significant increase in HDL-cholesterol (130). Figure 1 shows that adjustment for BMI by ANCOVA accounted for only 25% of the HDL-cholesterol difference between runners who ran under 16 $km \cdot wk^{-1}$ and those that exceeded 80 $km \cdot wk^{-1}$.

INTERVENTION STUDIES

In contrast to population (cross-sectional) studies, intervention studies show that runners' changes in HDL-cholesterol are strongly dependent on loss of weight. In one study, Wood et al. assigned men at random to vigorous exercise (primarily running, $N = 48$) or to control ($N = 33$) over a 1-yr period (132,134,139). Within the exercise group, changes in HDL-cholesterol were significantly correlated with weekly running distance ($r = 0.44$), changes in total body mass ($r = -0.53$), and changes in percent body fat ($r = -0.47$). Forty-six percent of the variance of the runners' HDL-cholesterol changes were accounted for by changes in body composition and running distance. However, when

TABLE 2. Population-based studies of the association of cardiorespiratory fitness with CVD or CHD.

Study	Adjustment for Adiposity
Canadian Health Survey 7-yr follow-up study in men and women (2)	Subjects who did not pass or who were ineligible for the Canadian home fitness test had significantly higher risk for CVD mortality than those that passed when adjusted for BMI, sex, age, and smoking (2).
Aerobic Center Longitudinal Study 8.32-yr follow-up of 10,224 men and 8.15-yr follow-up of 3120 women (6)	Longer treadmill test duration predicted significantly lower risk of CVD mortality in men. BMI ≥ 26.9 unrelated to all-cause mortality. Adjustment for BMI and other covariates did not eliminate the association between fitness and all-cause mortality (effects of adjustment not reported for cardiovascular mortality) (6).
Aerobic Center Longitudinal Study of 5.1-yr follow-up of 9777 men having two fitness measurements 4.9 yr apart (7)	Rates of CVD mortality were highest in men who were unfit at two visits (i.e., lowest quintile for treadmill test duration), intermediate in men who were fit at only one visit, and lowest in men who were fit at both visits. These differences were significant when adjusted for BMI and other covariates (7). (See caveat in 131.)
Aerobics Center Longitudinal Study 8.4-yr follow-up of 25,341 men and 7.5-yr follow-up of 7080 women (8)	The relative risk of CVD for fitness > 20th sample percentile was 0.37 for men (0.59 when adjusted for BMI and other covariates) and 0.36 for women (0.41 when adjusted) (both significant) (8).
Seattle Heart Watch study 5.6-yr follow-up of 2365 men (9)	Activity unrelated to CHD risk; however, a treadmill test duration of 6 min or less was associated with 12-fold increase in risk. Risk adjusted for age and BMI not reported (9).
Lipid Research Clinics Mortality Follow-up Study 8.5-yr follow-up of 3106 men (17)	Compared with the most fit men (defined by submaximal heart rate during a treadmill test), the least fit had 8.5 times higher rate of CHD and 6.5 times higher risk of CVD. Quetelet index unrelated to fitness and not included among covariates in multivariate adjustment (17).
Norwegian 9- to 11-yr follow-up of 1832 middle-aged men (18)	Risk of CHD deaths greatest for the lowest fitness quartile (i.e., cumulative work performed on a bicycle ergometer divided by body weight). No statistical test for trend, and no adjustment for adiposity (18).
Norwegian 12-yr follow-up of 1428 middle-aged men (19)	When adjusted for BMI and other covariates, the relative risks by quartile of fitness were 1.0, 0.66, 0.50 ($P < 0.05$), and 0.47 ($P < 0.05$) (19).
Aerobics Center Longitudinal Study 8.4-yr follow-up of 25,341 men (20)	When adjusted for age, fatal CVD rates decreased with increasing levels of fitness in men having a BMI < 27 kg · m^{-2} (14.5, 9.6, and 6.7 deaths per 10,000 man-years, $P = 0.001$), but not in those having a higher BMI (17.9, 10.6, and 9.5 deaths per 10,000 man-years, $P = 0.24$) (20).
Copenhagen Male Study 17-yr follow-up of 4999 men (31)	Among men who did a minimum of light physical activity for 4 h · wk^{-1}, survivors had higher baseline fitness (indirect estimates of $\dot{V}O_{2max}$ on cycle ergometers) than men who died from ischemic heart disease. BMI inversely related to cardiorespiratory fitness ($P < 0.001$) but not used in adjustment (31).
Kuopio Ischemic Heart Disease Risk Factor Study 4.9-yr follow-up of 1166 men (46)	Adjustment for BMI had minor impact on the relative risk of myocardial infarction in the highest vs lowest third of physical fitness (relative risk = 0.26–0.35). Significant both before and after adjustment (46).
Norwegian 7-yr follow-up of 2014 middle-aged men (56)	Risk of CHD deaths greatest for the lowest fitness quartile (difference among fitness quartiles, $P < 0.001$). No adjustment for adiposity (56).
4.8-yr follow-up of 2,779 Firemen and police men (77)	Men who were above the median fitness (highest work load sustained for 5 min on cycle ergometer) had 55% lower risk for systematic myocardial infarction. Significant when adjusted for other covariates (lean body mass not selected among covariates in stepwise procedure) (77).
Norwegian 15.9-yr follow-up of 1960 middle-aged men (91)	The highest fitness quartile (i.e., differences between observed and expected work capacity according to body weight) had 70% lower CVD risk than the least fit quartile ($P < 0.001$), which was decreased to 59% ($P = 0.01$) when adjusted for BMI and other risk factors (91).
U.S. Railroad Study 20-yr follow-up of 2431 men (104)	Men with lower exercise heart rates had lower death rates from CVD and CHD. BMI not included in proportional hazards regression analysis (104).
Belgian Physical Fitness Study 5-yr follow-up of 2109 men (106)	Interpolated physical working capacities per kilogram body weight was inversely related to ischemic heart disease both before and after adjustment for BMI and other risk factors. Mean BMI identical in men with and without ischemic events (106).

adjusted for changes in body composition, the runners' changes in HDL-cholesterol were no longer significantly related to weekly running distance (132).

A second study by this group compared the lipoprotein changes of men who dieted ($N = 42$), or exercised vigorously (primarily running, $N = 47$) to nondieting sedentary controls ($N = 42$) (135,140). All were sedentary and moderately overweight at baseline. During the 1-yr trial, the exercisers ran (mean ± SD) 18.9 ± 13.1 km·wk^{-1} and lost 4.0 ± 3.9 kg of body weight, whereas the controls' weights remained stable (mean gain of 0.6 ± 3.7 kg). Compared with mean changes in controls, the exercisers significantly increased their HDL-cholesterol levels (difference ± SE, 0.13 ± 0.03 mmol·L^{-1} or 5.05 ± 1.17 mg·dL^{-1}), but this difference was eliminated by adjustment for changes in BMI (0.04 ± 0.04 mmol·L^{-1} or 1.46 ± 1.44 mg·dL^{-1}). Within the exercise group, changes in HDL-cholesterol during the 1-yr study were correlated with running distances ($r = 0.45$) and changes in BMI ($r = -0.58$). Changes in HDL-cholesterol were no longer significantly correlated with running distance when adjusted for changes in BMI, whereas changes in BMI remained significantly correlated with the exercisers' changes in HDL-cholesterol ($r = -0.39$) when adjusted for weekly running distance.

In another study, Thompson et al. showed that weight loss was not required to achieve modest increases in HDL-cholesterol with exercise. They trained 17 sedentary men 4 hr·wk^{-1} while keeping both body weight and percent body fat constant over 1 yr by overfeeding (117). By the end of the study, HDL-cholesterol had increased by 0.1 mmol·L^{-1} (3.8 mg·dL^{-1}), caused primarily by a 33% increase (0.06 mmol·L^{-1} or 2.3 mg·dL^{-1}) in HDL2. However, the maintenance of body weight through overfeeding does not reflect the usual condition of men who exercise vigorously. Significant loss of total weight and percent body fat occurs usually within the first 6 months of training. The contribution of weight loss to lipoprotein levels in these 17 men was investigated through further experimentation by Thompson and colleagues (113). On completion of the 1-yr weight stable phase; the 17 men were assigned at random to either a weight stable group (i.e., continuing the previous year's protocol) or a weight loss group. The lipoprotein changes in the weight stable group were not sustained by 18 months, i.e., HDL-cholesterol decreased 0.05 mmol·L^{-1} (2.0 mg·dL^{-1}) and

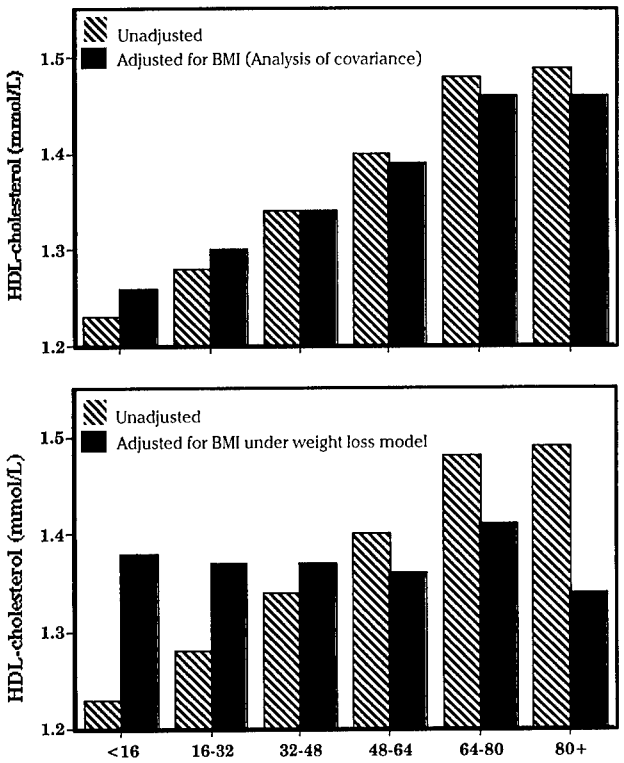


FIGURE 1—Distribution of mean plasma HDL-cholesterol concentrations by reported weekly distance run in 7059 male runners (130). Upper panel: *Solid bars* show the effects of adjustment by traditional analysis of variance, which uses the cross-sectional relationship between BMI and HDL-cholesterol to adjust for weight differences between distance groups. Bottom panel: *Solid bars* show the effects of using the coefficient relating weight loss to HDL-cholesterol changes (4.28 mg·dL^{-1} per unit decrease in BMI) (126) to adjust for weight differences between distance groups.

HDL2-cholesterol decreased 0.03 mmol·L^{-1} (1.3 mg·dL^{-1}). The weight loss group lost 9.4 kg, resulting in additional increases of 0.8 mmol·L^{-1} (3.3 mg·dL^{-1}) in HDL-cholesterol and 0.11 mmol·L^{-1} (4.3 mg·dL^{-1}) in HDL_2-cholesterol concentrations. This suggests that at the end of the 18-month period, weight loss accounted for most of the increases in plasma HDL-cholesterol (75%) and HDL2 (85%) from baseline.

These results suggest that the increases in HDL in sedentary men who begin exercising vigorously arise primarily from processes associated with weight loss. They agree with observations by Katzel et al. and Sopko et al. showing only small changes in HDL-cholesterol in the absence of weight change (40,107), and with the observations by Leon et al. that training-induced changes in HDL-cholesterol are related to changes in percent body fat but not $\dot{V}O_{2max}$ (51).

Previously obese runners. If HDL-cholesterol levels in runners are principally related to historical weight loss rather than current adiposity levels, then previously obese runners would be expected to have higher HDL-cholesterol than runners who were always lean. In one study, we found that HDL-cholesterol concentrations were unrelated to training level or running performance, but strongly related to the difference between the runners' greatest and current BMI. HDL-cholesterol levels were increased 3.0 mg·dL^{-1} for every kilogram per square meter below greatest weight. This association largely reflected the elevated HDL-cholesterol levels of five men who lost more than 6 kg·m^{-2} since their greatest weight (126). The association between weight history and lipoprotein concentrations was also examined in the National Runners' Health Study (129). Current HDL-cholesterol levels were greatest in those runners with the greatest weight loss since their maximum lifetime weight, as well as the runners with the greatest reductions in circumference of their waist, hip, and chest since their maximum weight. These results remained significant when adjusted for current BMI and running mileage.

The trouble with statistics. The intervention studies suggest a prominent role for the metabolic processes associated with weight loss in the etiology of the runners' lipoprotein profiles. Thus, it would be misguided to dismiss the importance of these processes simply because the HDL differences in population studies persist when statistically adjusted for BMI. It may also be misguided to dismiss the importance of weight loss in lowering CHD and CVD risk among active individuals. However, there are no intervention studies having CHD or CVD as endpoints to provide guidance on this issue.

There are the obvious limitations to statistical adjustment for BMI in population studies. The adjustment for indices of weight for height (including BMI) are valid only to the extent that these measures reflect the biologically relevant parameters of body fat. Measurement error associated with BMI may also reduce its effectiveness of the covariate. Some reports cite evidence of interactions between fitness and weight and between activity and weight in their relationship to disease that is contrary to the statistical models (48,69). However, a more fundamental issue concerns the meaning of statistical adjustment and the assumptions made in its calculation. As traditionally applied, the adjustment uses the cross-sectional relationships between weight and the health outcomes. It therefore invokes a frame of reference of a population that is static in time. This is appropriate if the leanness of physically active individuals is because of self-selection, i.e., if lean individuals take up sports and lead more physically active lives than overweight men and women. For example, it is apropos to conduct comparisons of bus drivers and conductors, since London bus drivers are heavier when hired than conductors (66). As applied to Tables 1 and 2, the statistical adjustments suggest that CHD, CVD, and lipoprotein differences between active and inactive men are not simply the consequence of lean and healthy subjects choosing to be active whereas overweight unhealthy subjects lead sedentary lives (i.e., they rule out the effects of self-selection).

A separate issue is whether the metabolic processes associated with weight loss produce the high HDL-cholesterol levels of runners. For this, the static model requires justification. Vigorous physical activity causes loss of weight and body fat (138–140). Higher mileage runners are leaner because they have lost more weight or avoided weight gain. Although lean individuals may be more likely to take up running as a sport (self-selection), the leanness of runners is

also caused in large measure by weight loss as a consequence of running. The validity of using weight as a covariate in ANCOVA, logistic regression, or survival analysis depends critically on whether the cross-sectional relationship between weight and health outcomes can be used to estimate the dynamic effects of weight loss on these health outcomes.

This critical assumption has been shown to be invalid for plasma HDL-cholesterol concentrations. We have found that initially sedentary men who began running were able to increase their HDL cholesterol by 0.11 $mmol \cdot L^{-1}$ (4.28 $mg \cdot dL^{-1}$) for each unit decrease in BMI over the 1-yr study (135). This change in HDL-cholesterol is fivefold greater than the cross-sectional data implied at baseline (0.02 $mmol \cdot L^{-1}$ or 0.78 $mg \cdot dL^{-1}$ increase per unit decrease in BMI) or at the end of the 1-yr study (0.01 $mmol \cdot L^{-1}$ or 0.57 $mg \cdot dL^{-1}$ increase per unit decrease in BMI). This suggests that standard epidemiological methods for adjusting for weight are likely to seriously underestimate the confounding effects of weight loss.

Studies carried out by our group suggest that expected HDL-cholesterol for a given weight depends in part on whether the current weight is relatively high or low within the historical range of weights experienced by the individual. Williams compared the cross-sectional HDL levels of runners with their current weights (as traditionally used for adjustment) and their weight loss since they began running 1 yr ago (127). In all cases, current BMI showed little relationship to current HDL levels, which is consistent with the conclusions of most population studies. However, there was a strong relationship between previous weight loss since starting to run and current HDL levels. Thus, the actual relationship depends on past weight history in addition to current weight (126,127,136). Runner A could be heavier than runner B but have higher HDL-cholesterol than B if A had lost more weight than person B. This supposes a frame of reference within each person, a frame of reference also invoked when postulating the existence of a weight set point (126,127).

Reassessing statistical adjustment. ANCOVA uses the following method of correction. To correct for differences in BMI, the mean differences in BMI between runners and nonrunners is multiplied by the expected change in HDL per unit difference in BMI. This value is then subtracted from the mean difference in HDL-cholesterol to get the corrected mean difference, i.e., (average HDL-cholesterol difference) $-$ $\beta \times$ (average BMI difference), where β is the expected HDL difference per unit difference in BMI. ANCOVA uses the cross-sectional (static) relationship between HDL-cholesterol and BMI to estimate β. For example, we have reported that average HDL-cholesterol concentrations were 0.39 $mmol \cdot L^{-1}$ (15.33 $mg \cdot dL^{-1}$) higher in runners than sedentary men and that the runners were also 2.48 $kg \cdot m^{-2}$ leaner (133). Cross-sectionally, we found that HDL-cholesterol was 0.03 $mmol \cdot L^{-1}$ (1.065 $mg \cdot dL^{-1}$) higher for each unit decrease in BMI ($\beta = -1.065$ $mg \cdot dL^{-1} \cdot kg^{-1} \cdot m^{-2}$). Thus, the standard application of ANCOVA suggests that only 0.07 $mmol \cdot L^{-1}$ (2.64 $mg \cdot dL^{-1}$) of the difference was because of BMI, and that 0.33 $mmol \cdot L^{-1}$ (12.69 $mg \cdot dL^{-1}$) was the corrected difference between runners and nonrunners, i.e., (15.33 $mg \cdot dL^{-1}$) $-$ (-1.065 $mg \cdot dL^{-1} \cdot kg^{-1} \cdot m$) $\times$ (-2.48 $kg \cdot m^{-2}$). However, if we use the coefficient for weight loss (-0.11 $mmol \cdot L^{-1}$ or -4.28 $mg \cdot dL^{-1}$) to estimate how a one-unit difference in BMI affects HDL, then 0.27 $mmol \cdot L^{-1}$ (10.61 $mg \cdot dL^{-1}$) of the difference is because of BMI, and that 0.12 $mmol \cdot L^{-1}$ (4.6 $mg \cdot dL^{-1}$) is the corrected difference between runners and nonrunners, i.e., (15.33 $mg \cdot dL^{-1}$) $-$ (-4.28 $mg \cdot dL^{-1} \cdot kg^{-1} \cdot m^{-2}$) $\times$ (-2.48 $kg \cdot m^{-2}$). The choice of models very much affects the conclusion reached about exercise versus body fat. The traditional (static) ANCOVA model suggests that metabolic processes associated with BMI have minor roles (17%) in producing high HDL in runners, whereas the weight loss model predicts the metabolic processes associated with BMI are pivotal (i.e., accounting for 70%).

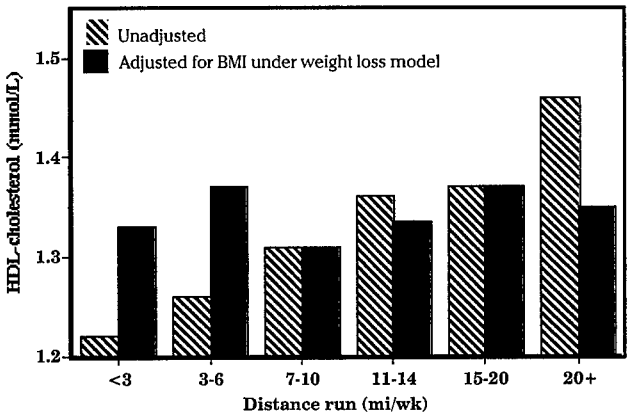


FIGURE 2—Distribution of mean plasma HDL-cholesterol concentrations by reported weekly distance run in 2906 male runners (43). *Solid bars* show the effects of using the coefficient relating weight loss to HDL-cholesterol changes (4.28 $mg \cdot dL^{-1}$ per unit decrease in BMI) (126) to adjust for weight differences between distance groups. Ninety-two percent of the HDL-cholesterol difference between the high- and low-distance runners (0.24 $mmol \cdot L^{-1}$) can be explained by the 2 $kg \cdot m^{-2}$ difference in their mean BMI (2 $kg \cdot m^{-2} \times 0.11$ $mmol \cdot L^{-1} \cdot kg^{-1} \cdot m^{-2} = 0.22$ $mmol \cdot L^{-1}$).

In another example (Fig. 1, upper panel), the traditional (static) ANCOVA model suggested that only 25% of the HDL-cholesterol difference between high-mileage and low-mileage runners was explained by BMI. In contrast, the dynamic weight loss model (i.e., 4.28 $mg \cdot dL^{-1}$ increase per kilogram per square meter of weight loss) eliminates all of the differences in HDL-cholesterol between high- and low-mileage runners (Fig. 1, lower panel). We also estimate that 92% of the HDL-cholesterol difference reported in the other large study of lipoproteins in runners is attributable to their difference in BMI (Fig. 2). Finally, elsewhere we have plotted the HDL-cholesterol differences reported in 23 published cross-sectional comparisons between runners and sedentary controls against their predicted differences on the basis of our model. Assuming that all of the HDL-cholesterol differences are the consequence of the metabolic processes associated with the lower body weights of the runners, the model predicts with a high correlation the published differences between runners and sedentary men (r = 0.80) (132).

The above examples demonstrate that standard statistical adjustment by ANCOVA may substantially underestimate the effects of weight on the lipoprotein profiles of runners. Running is a vigorous activity, and it is not possible to determine to what extent our findings apply to population studies of total physical activity and CHD and CVD. Some studies attribute the lower CHD and CVD risk in active individuals to vigorous activity alone, others negate any advantage of vigorous over nonvigorous activity, and still others assign greater risk reduction to vigorous activity although recognizing the contribution of moderate intensity activity. The relationship between disease risk and weight history is seldom reported. One study that did, by Paffenbarger et al., found a significant dose-response relationship between exercise and CHD risk when adjusted forweight gain since college (75). However, even this may not be an appropriate measure of the difference betweena person's current weight and their expected sedentaryweight because even long-distance runners appear to gain weight as they age (128).

FUTURE RESEARCH PRIORITIES

Population studies that examine disease endpoints will forever be restricted to measurements of adiposity that are practical for large samples. These measurements are adequate for testing whether the associations observed between disease and physical activity are the artifact of self-selection for weight, but not for testing whether metabolic processes associated with weight loss are involved in the etiology of the disease (e.g., dyslipoproteinemias and physical activity). This will require detailed studies of the physiological mechanisms responsible for these health outcomes in runners and other physically active individuals.

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Dose-response: variation with age, sex, and health status

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ABSTRACT

WILMORE, J. H. Dose-response: variation with age, sex, and health status. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S622–S634. **Purpose:** The purpose of this study was to summarize the literature on the influence of age, sex, and health status on the changes in systolic (SBP) and diastolic blood pressure (DBP), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) consequent to exercise training. **Methods:** A MEDLINE search was performed from January 1966 through August 2000 to identify studies that have investigated the effects of age, sex, and health status on the changes in the outcome variables with exercise training. References from these studies and from review and meta-analysis studies were also reviewed. **Results and Conclusions:** The results indicate that age has little or no influence on the changes in SBP, DBP, TG, and HDL-C in response to exercise training. When looking at sex, females appear to have an attenuated response to exercise training compared with males with respect to SBP, DBP, and HDL-C, but the data for TG are equivocal. Finally, there appears to be more favorable changes in resting SBP and DBP, TG, and HDL-C in unhealthy subjects (hypertensive and post-MI patients) when compared with healthy subjects. **Key Words:** EXERCISE TRAINING, RESTING SYSTOLIC AND DIASTOLIC BLOOD PRESSURE, RESTING TRIGLYCERIDES AND HDL-C, HYPERTENSIVES VERSUS NORMOTENSIVES, POST-MI VERSUS HEALTHY

It has become widely accepted that a physically active lifestyle promotes good health and reduces the risk of chronic disease and disability (6,13,36,37). It is less clear as to what levels of activity are necessary to optimize these benefits. In 1995, the Centers for Disease Control and Prevention in collaboration with the American College of Sports Medicine (ACSM) introduced a radical change in how we view the dose of exercise necessary for health promotion and disease prevention (37). A panel of experts reviewed the pertinent physiological, epidemiological, and clinical evidence and came up with the following concise public health message: "Every U.S. adult should accumulate 30 min or more of moderate-intensity physical activity on most, preferably all, days of the week" (37). The scientific basis for this new statement had been clearly established by Dr. William L. Haskell, in the 1993 ACSM Wolffe Lecture published in 1994 (21). Many clinicians, researchers, and the lay public had previously subscribed to the believe that a substantially higher dose of exercise was necessary in order to obtain the health-related benefits, and the ACSM Position Stand on "The Recommended Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory and Muscular Fitness in Healthy Adults" (1) was used to support their beliefs. Although there is not a large database to support this new statement, it was adopted by the NIH (36) and the Surgeon General (6). The new statement, however, is not without its critics (54), and many scientists are presently engaged in researching the benefits of cumulative brief bouts of lower intensity exercise.

With this as background, the present article investigates the dose-response relationship and its variation with age, sex, and health status. Since this symposium explores many outcome variables, it was not practical to conduct an analysis of each of these variables with respect to age, sex, and health status. Therefore, a decision was made to focus on blood pressure, including systolic (SBP) and diastolic blood pressure (DBP), and blood lipids and lipoproteins, specifically triglycerides (TG) and HDL-cholesterol (HDL-C).

METHODS

An attempt was made to review every article that had been published on the changes in blood pressure and lipids and lipoproteins consequent to exercise training as specifically related to age, sex, and health status. It was immediately evident that a strategy had to be developed to limit the scope of this review. With this in mind, studies were selected by priority as follows: 1) studies specifically investigating the influence of age, sex, or health status on the training response; 2) studies investigating a specific age (adolescents, adults, older adults), sex (male or female), and health status (diseased or healthy); and 3) in areas where there were too many studies (i.e., studies on blood pressure and/or lipid and lipoprotein changes in adults, or studies on a diseased population), reliance was placed on detailed reviews and meta-analyses.

Attempts were made to locate randomized controlled trials when available, but this was not always possible.

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TABLE 1. Effect of age on the magnitude of change in resting blood pressure consequent to exercise training.

Study, Country	Study Design and Population	Training Program	Results	Comments
Adolescents				
Dwyer et al., 1983 (8) Australia	Random assignment of 5th grade (10-yr-olds) to one of three groups: endurance fitness group, skill group, control group; N ≥ 500 boys and girls (actual number not specified).	Endurance fitness group had 1.25 hr·d^{-1} of endurance activities daily; skills group had 1.25 h·d^{-1} of skill activities; control group had 30 min of physical education 3 d·wk^{-1} for 14 wk.	Physical work capacity ↑ significantly only in the endurance fitness group, but there were no significant changes in resting blood pressure in any of the three groups.	This was not a well-controlled study, with few details provided.
Fisher and Brown, 1982 (12) USA	Seventh grade boys and girls (N = 38) were randomly assigned to exercise, exercise + diet, diet and control groups.	12 wk of vigorous activity, 30 min·d^{-1}, 5 d·wk^{-1} (no other details provided).	There was a significant ↑ in treadmill time and fitness scores in the exercise groups. However, SBP did not change in either exercise (or diet) group; DBP ↓ 6.4 mm Hg in the exercise group.	These data have appeared only in a published abstract.
Hagberg et al., 1983 (17) USA	Nonrandom selection from a hypertensive population (>95th percentile): N = 19 boys and N = 6 girls with a mean age of 15.6 yr	Endurance activity for 30–40 min·d^{-1}, 3 d·wk^{-1}, at 60–65% of $\dot{V}O_{2max}$ for 6 mo.	There was ~10% ↑ in $\dot{V}O_{2max}$ and significant ↓ in SBP and DBP of 8 and 5 mm Hg, respectively.	Note: This was a hypertensive population defined as >95th percentile for age.
Hansen et al., 1991 (20) Denmark	Randomized selection of 64 hypertensive (H; ≥95th percentile) and 68 normotensive (N) boys and girls 9–11 yr old from 1369 children; each BP group was randomized into training or control subgroups by sex.	The training group received three extra 50-min sessions of PE per week for 8 mo. The program consisted of games, gymnastics and exercises.	$\dot{V}O_{2max}$ ↑ by 8.4% and 4.9% (N) and 4.0% and 3.5% (H) for boys and girls, respectively. Adjusted SBP/DBP ↓ by 6.5/4.1 mm Hg (N) and 4.9/3.8 mm Hg (H) training groups.	The changes with training were not noted at 3 mo, only at 8 mo. Further, there were no sex differences at the end of the training period, but sex had a significant effect in the hypertensive group, with girls exhibiting no change in SBP.
Linder et al., 1983 (30) USA	Random assignment to exercise or control group; N = 50 boys 11–17 yr old.	8-wk progressive walk-jog exercise program, 30 min·d^{-1}, 4 d·wk^{-1} at an intensity of up to 80% of HR_{max}.	Physical working capacity ↑ 15.2% in the exercise group with no change in the control group; there were no changes in resting blood pressure in either group.	The purpose of this study was to observe changes in lipids and lipoproteins. There was no obvious attempt to control blood pressure measurements.
Young and Middle-Aged Adults				
Fagard, 1999 (9) Belgium	A meta analysis was conducted on a total of 44 randomized controlled trials investigating the effect of dynamic aerobic endurance exercise on resting blood pressure in otherwise healthy normotensive and hypertensive individuals.	From the 44 studies, 68 exercise groups were identified. Median for age, 44 yr; study duration, 16 wk; frequency, 3 d·wk^{-1}; session duration, 50 min; training intensity, 65% of $\dot{V}O_{2max}$.	$\dot{V}O_{2max}$ ↑ by 11.8%, SBP/DBP ↓ 3.4/2.4 mm Hg for all groups. Normotensive group, SBP/DBP ↓ 2.6/1.8 mm Hg; hypertensive group, SBP/DBP ↓ 7.4/5.8 mm Hg. Note: These are weighted mean values after adjustment for control values.	Age was not found to be a significant determinant of the blood pressure response to training. Further, all blood pressure changes were independent of changes in body weight.
Halbert et al., 1997 (19) Australia	A meta-analysis was conducted on a total of 29 randomized trials of normotensive and hypertensive individuals. Of the total number of trials, 26 used aerobic training, two used resistance training, and one used a combination of aerobic and resistance training.	A total of 1533 participants (exercise and controls) comprised the study group. Age ranged from 18–79 yr. Means for program characteristics were study duration, 19 wk; frequency, 3.2 d·wk^{-1}, session duration, not specified; 62% of $\dot{V}O_{2max}$.	There was no report of the mean change in exercise capacity, e.g., $\dot{V}O_{2max}$. SBP/DBP ↓ 4.7/3.1 mm Hg on average in those subjects aerobically trained, but there were no changes in those who resistance trained.	Age was not investigated as a potential mediator of the blood pressure response to training. The ↓ in BP in those trained aerobically was independent of intensity and frequency of training.
Kelley and Tran, 1995 (26) USA	A meta-analysis was conducted on a total of 35 randomized trials of normotensive individuals.	The 35 studies included 51 exercise groups (800 subjects) and 23 control groups (276 subjects). Means for exercise groups' age, 35 yr; study duration, 15 wk; frequency, 3.5 d·wk^{-1}; session duration, 37 min; training intensity, 77.3% of HR_{max}.	$\dot{V}O_{2max}$ ↑ by 14.5% and SBP/DBP ↓ 4.4/3.2 mm Hg for all groups.	Age was not investigated as a potential mediator of the blood pressure response to training.

Many of the studies included in this review were not truly randomized, and some were strictly observational studies. However, several of the nonrandomized, observational trials with no control groups were tightly controlled, using repeated measures of the outcome variables both before and after the exercise training period, and included large numbers of subjects. A MEDLINE search was conducted for all training studies in which either or both blood pressure and blood lipids and lipoproteins were the outcome variables. The database extended from January, 1966 through August 2000. The reference list from each article obtained in the MEDLINE search was then screened for additional studies. Review articles concerning the responses of blood pressure and blood lipids and lipoproteins to exercise training were also obtained and their reference lists were also screened for additional studies. In several cases where the identified article was not clear on whether comparisons were conducted across age groups or for males versus females,

TABLE 1. *Continued*

Study, Country	Study Design and Population	Training Program	Results	Comments
Older and Elderly Adults				
Braith et al., 1994 (3) USA	Stratified random assignment (on basis of initial $\dot{V}O_{2max}$) of 44 normotensive, sedentary men and women, 60–79 yr old, to moderate intensity (MI, 70% maximal heart rate reserve (MHRR)), high intensity (HI, 80–85% MHRR), or control groups.	6-mo endurance training program, 3 d·wk^{-1}, with duration increased up to 45 min·d^{-1} in MI group and 35 min·d^{-1} in HI group during the last 13 wk of the study; treadmill walking with grade.	$\dot{V}O_{2max}$ ↑ by 16.0% and 26.9% in the MI and HI groups respectively; SBP ↓ from 121 to 112 mm Hg in MI and from 120 to 112 mm Hg in HI; DBP ↓ from 72 to 64 mm Hg in MI and from 75 to 68 mm Hg in HI with NS between groups.	These changes in BP occurred without changes in body weight.
Cononie et al., 1991 (7) USA	Random assignment of 56 normotensive to moderately hypertensive men and women, 70–79 yr old, to control, resistance training or endurance training groups.	6-mo training program of resistance (RT) or endurance training (ET), 3 d·wk^{-1} of increasing intensity. ET exercised 20–30 min·d^{-1} at 50% $\dot{V}O_{2max}$ initially, building to 35–45 min·d^{-1} at 75–85% $\dot{V}O_{2max}$ for the last 2 mo. RT trained on 10 different exercise machines using progressive resistance training.	Upper body strength ↑ 18% in RT group and $\dot{V}O_{2max}$ ↑ by 20% in ET group; resting BP did not change in RT group, but ↓ in ET group (DBP ↓ 5 mm Hg).	In those with pretraining BP of >140/90, ET reduced SBP by 8 mm Hg and DBP by 9 mm Hg. Sex differences were not analyzed.
Young Adult vs Older Adult				
Meredith et al., 1989 (33) USA	Volunteers, N = 10 elderly (mean age, 65.1 yr; 5 men and 5 women) and N = 10 young (mean age, 23.6 yr; 5 men and 5 women), who were sedentary and healthy.	Trained 3 d·wk^{-1}, 45 min·d^{-1} on cycle ergometers at 70% of heart rate reserve (~70% of $\dot{V}O_{2max}$) for a period of 12 wk.	$\dot{V}O_{2max}$ ↑ 12.1% and 19.9% in the young and old subjects, respectively; resting SBP and DBP did not change in either group.	Blood pressure was not the focus of this study, and the details of the measurement protocol were not provided. Sex differences were not analyzed.
Wilmore et al., 2000 (55) USA	The HERITAGE Family Study: Volunteers (N = 507) included black and white men and women, 17 to 65 years of age. No control group was used.	Trained 3 d·wk^{-1} for a total of 60 exercise sessions on cycle ergometers, starting at 55% of $\dot{V}O_{2max}$ for 30 min per session and building to 75% of $\dot{V}O_{2max}$ for 50 min per session for the last 6 wk.	$\dot{V}O_{2max}$ ↑ 17.4%; there were small but significant (i.e., <3 mm Hg) ↓ in resting SBP, which varied by race and sex, but not by age. DBP remained unchanged.	

authors were contacted directly to obtain the missing information. This review attempts to determine if age, sex, or health status affects the response to a given dose of exercise on each of the selected outcome variables.

RESULTS

The results of this review are presented in two sections: Blood Pressure and Blood Lipids and Lipoproteins. They are presented in table format, with Tables 1–3 dealing with the influence of age, sex, and health status, respectively, on the effect of exercise training on changes in blood pressure. Tables 4–6 address the influence of age, sex, and health status, respectively, on the effect of exercise training on changes in blood lipids and lipoproteins. Age was divided into the following categories: children and adolescents, young and middle-aged adults, and older and elderly adults. Sex was divided into male and female, and health status was divided into hypertensive versus normotensive for blood pressure, and no known coronary artery disease versus myocardial infarction (MI) for lipids and lipoproteins. There were several exceptions to these categories, but the rationale for including these exceptions will be provided.

Each table consists of five columns: study (author, year, and reference number) and country of origin; study design and subject population; training program details; results of the study; and comments on important aspects of the study. In the results column, attempts were made to define the effectiveness of the training program. Most of the studies presented in Tables 1–6 used aerobic endurance training as their mode of training. In most cases, authors provided the average increase in maximal oxygen uptake ($\dot{V}O_{2max}$), whereas others provided increases in some measure of physical working capacity. For those studies using resistance training, average increases in strength are included when provided by the authors.

Blood Pressure

Effect of age. Table 1 presents the available data on the blood pressure response to exercise training as affected by age. First, not all studies have demonstrated significant

TABLE 2. Effect of sex on the magnitude of change in resting blood pressure consequent to exercise training.

Study, Country	Study Design and Population	Training Program	Results	Comments
Adolescents				
Hagberg et al., 1983 (17) USA	(See Table 1 for details)	(See Table 1 for details)	(See Table 1 for details)	The reduction in BP was more pronounced in boys.
Hansen et al., 1991 (20) Denmark	(See Table 1 for details)	(See Table 1 for details)	(See Table 1 for details)	There were no sex differences in response to training in the normotensive groups, but sex had a significant effect in the hypertensive groups; girls exhibited no change in SBP.
Young and Middle-Aged Adults				
Kelly, 1999 (27) USA	A meta-analysis was conducted on a total of 10 randomized clinical training studies on women (732 subjects: 504 exercise, 228 control).	There were a total of 19 exercise groups and 10 control groups. Means for exercise groups: age, 53 yr; study duration, 31 wk; frequency, 4 $d \cdot wk^{-1}$; session duration, 39 min; training intensity, 63% of $\dot{V}O_{2max}$.	$\dot{V}O_{2max}$ ↑ by an average of 14% across the training studies. SBP ↓ an average of 2 mm Hg and DBP ↓ an average of 1 mm Hg.	The author concluded that the mean reductions in resting BP consequent to exercise training appear to be somewhat less in women compared with men on the basis of meta-analytic studies of samples of mostly men (i.e., SBP/DBP reductions of −4/−3 in men and −2/−1 in women.
King et al., 1991 (28) USA	Random assignment to one of four groups: higher intensity group-based training (HI-G); higher intensity home-based training (HI-H); lower intensity home-based (LI-H); and control. Men (N = 197) and women (N = 160), 50 to 65 yr old, sedentary, and free of CVD.	HI training groups exercised 3 $d \cdot wk^{-1}$, 40 $min \cdot d^{-1}$, at 73–88% of peak treadmill heart rate for a period of 12 mo; LI training group exercised 5 $d \cdot wk^{-1}$, 30 $min \cdot d^{-1}$, at 60–73% of peak treadmill heart rate.	$\dot{V}O_{2max}$ ↑ by 5.9% and 2.5% (HI-G); 4.0% and 6.1% (HI-H); and 4.6% and 4.0% (LI-H) for men and women, respectively. No significant changes in resting blood pressure were found at 6 or 12 mo in the exercise groups compared to the control groups.	There were no reported sex differences in response.
Wilmore et al., 2000 (55) USA	(See Table 1 for details)	(See Table 1 for details)	(See Table 1 for details)	SBP and DBP did not decrease in women, whereas SBP decreased in men.
Wood et al., 1991 (56) USA	Random assignment of moderately overweight men (N = 132) and women (N = 132), 25–49 yr of age, to one of 3 groups: control; hypocaloric NCEP diet; and hypocaloric NCEP diet + exercise. Subjects were previously sedentary and free of CVD.	The diet + exercise group performed brisk walking and jogging 3 $d \cdot wk^{-1}$, building to at least 45 $min \cdot d^{-1}$, at an intensity of 60–80% of HR_{max} for a period of 12 mo.	$\dot{V}O_{2max}$ ↑ by 25.2% in men and 23.7% in women. Resting SBP/DBP ↓ 4.1/2.4 mm Hg and 4.1/2.2 mm Hg in the diet-only group and 5.4/4.9 mm Hg and 3.6/2.0 mm Hg in the diet + exercise group in men and women, respectively.	Resting SBP and DBP were ↓ in both intervention groups compared with control, but did not differ between intervention groups. It is likely that the blood pressure reductions were more related to the weight loss associated with the diet (4–5 kg in all intervention groups) than exercise.
Older and Elderly Adults				
Braith et al., 1994 (3) USA	(See Table 1 for details)	(See Table 1 for details)	(See Table 1 for details)	Men and women responded to endurance training with similar changes in BP.

decreases in either or both SBP and DBP with training, but those studies reporting no change are in the minority. Furthermore, they appear across all groups. For the majority of studies where blood pressure decreases were reported consequent to training, the magnitude of change appears to be comparable across age groups. Unfortunately, only two studies actually compared age groups (33,55), one reporting no changes in blood pressure in either the younger or older groups (33) and the other reporting only small changes in the younger and older groups (55). Overall, it appears that there is an equivalent decrease in both SBP and DBP across age groups, which is in agreement with a recent review by Fagard (9). The magnitude of decrease varies, but would generally be in the range of 3–8 mm Hg for SBP and 2–6 mm Hg for DBP (Evidence Category B).

Effect of sex. Table 2 presents the available data on the blood pressure response to exercise training as affected by sex. Several of the studies reported no decreases in either or both SBP and DBP, but most reported decreases. In those studies reporting decreases, there appears to be a slightly greater response in boys and men when compared with girls and women, in agreement with the conclusion of Kelley (27), who had conducted a meta-analysis of a total of 10 training studies on women. The magnitude of decrease in blood pressure in boys and men was similar to that reported for age in the previous paragraph, whereas women were, on average, 1–3 mm Hg lower in their response (Evidence Category C).

Effect of health status. Table 3 presents the available data on the blood pressure response to exercise training as affected by health status. Although one study found no change in SBP or DBP after training (15) and another found the blood pressure decreases to be less in adolescent hypertensives compared with normotensives (20), most of the studies showed a greater decrease in both SBP and DBP in hypertensives when compared with normotensives. Fagard and Tipton's review chapter (10), which included a meta-analysis of all studies conducted before 1994, estimated that SBP/DBP decreases in normotensives were approximately −3/−3 mm Hg compared with −6/−7 mm Hg in borderline

TABLE 3. Effect of health status (hypertensive vs normotensive) on the magnitude of change in resting blood pressure consequent to exercise training.

Study, Country	Study Design and Population	Training Program	Results	Comments
Adolescents				
Hansen et al., 1991 (20) Denmark	(See Table 1 for details)	(See Table 1 for details)	SBP/DBP ↓ significantly by 6.5/4.1 mm Hg in the normotensive training group and by 4.9/3.8 in the hypertensive training group. (See Table 1 for details)	There were no changes at 3 mo, but only at 8 mo of training.
Young and Middle-Aged Adults				
Gilders et al., 1989 (15) USA	Subjects were recruited from the local community and screened for major pathology. A total of 29 subjects were recruited and 21 completed the study; 8 borderline/mild hypertensives (DBP > 84 mm Hg and <104 mm Hg) and 13 normotensives. There was an 8-wk control (C) period, 16-wk of endurance training (ET), and 12-wk of detraining (DT).	The C period started with exposure to cycle ergometer training 2 d·wk^{-1} for 10 min·d^{-1} during 1st wk to 30 min·d^{-1} during 8th wk at an intensity ~35% of $\dot{V}O_{2max}$. During the ET period, frequency was 3 d·wk^{-1}, duration was 30 min·d^{-1}, and intensity was ~70% of $\dot{V}O_{2max}$. All formal training activity stopped during DT.	$\dot{V}O_{2max}$ ↑ by 18% in the hypertensives and by 9% in the normotensives (Note: the hypertensive group gained some during the C period). It ↓ back to C period levels at the conclusion of the DT period. Resting BP and 24-h ambulatory BP did not change during either the ET period or the DT period in either group.	Although the total number of subjects in this study was small, the study was very well controlled.
Fagard and Tipton, 1994 (10) Belgium	Comprehensive review chapter of a meta-analysis of studies published prior to 1994.	See review paper for details.	The mean weighted net change in blood pressure (SBP/DBP) with endurance training was −3/−3 mm Hg in normotensive subjects, −6/−7 mm Hg in borderline hypertensive subjects and −10/−8 mm Hg in hypertensive subjects.	The change in resting blood pressure with resistance training was negligible. The authors stated that animal studies support the trends in humans for the most part.
Fagard, 1999 (9) Belgium	(See Table 1 for details)	(See Table 1 for details)	$\dot{V}O_{2max}$ ↑ by 11.8%, SBP/DBP ↓ 3.4/2.4 mm Hg for all groups.	In the normotensive group SBP/DBP ↓ 2.6/1.8 mm Hg and in the hypertensive group SBP/DBP ↓ 7.4/5.8 mm Hg. Note: These are weighted mean values after adjustment for control values.
Halbert et al., 1997 (19) Australia	(See Table 1 for details)	(See Table 1 for details)	There was no report of the mean change in $\dot{V}O_{2max}$. SBP/DBP ↓ 4.7/3.1 mm Hg on average.	There were no differences in the resting blood pressure responses to exercise training between normotensive and hypertensive subjects.
Older and Elderly Adults				
Cononie et al., 1991 (7) USA	(See Table 1 for details)	(See Table 1 for details)	Upper body strength ↑ 18% in RT group and $\dot{V}O_{2max}$ ↑ by 20% in ET group; resting BP did not change in RT group, but ↓ in ET group (DBP ↓ 5 mm Hg)	In those with pretraining BP >140/90, ET reduced SBP by 8 mm Hg and DBP by 9 mm Hg.
Hagberg et al., 1989 (18) USA	Hypertensive patients (N = 33), 60–69 yr old, were randomized to one of the following groups: control, low-intensity exercise (LI), moderate-intensity exercise (MI).	9-mo training program of low (1-h walk, 50% $\dot{V}O_{2max}$) or moderate intensity exercise (70–85% $\dot{V}O_{2max}$, 45–60 min·d^{-1}), 3 d·wk^{-1}; total kcal expended per day were equal for two groups	$\dot{V}O_{2max}$ ↑ by 28% in moderate-intensity (MI) group, but did not change in low-intensity (LI) group; SBP ↓ 20 mm Hg after training in the LI group and 8 mm Hg (ns) in the MI group and DBP ↓ 11–12 mm Hg in both training groups.	Low-intensity training clearly had a greater effect on SBP in this study, and the effects on DBP were essentially the same with both intensities of training.
Motoyama et al., 1998 (35) Japan	Hypertensive patients (N = 26, 12 men and 14 women) 64–84 yr of age volunteered to participate, 13 in the training group and 13 in the control group (6 men and 7 women in each group)	Walked on a treadmill at lactate threshold 30 min·d^{-1}, 3 to 6 d·wk^{-1} for a total of 9 mo.	There were no measures of change in aerobic capacity after training; SBP ↓ 15 mm Hg and DBP ↓ 9 mm Hg in the training group after the 9-mo training program.	Sex differences were not analyzed.
Seals and Reiling, 1991 (44) USA	Hypertensive subjects aged 50 to 74 yr were placed in an exercise training group (9 men and 5 women) or nonexercising control group (10 men and 2 women)	6-mo low intensity (40–50% of their heart rate reserve) aerobic training, 3 d·wk^{-1} for at least 30 min·d^{-1}	$\dot{V}O_{2max}$ ↑ 7% in the training group; SBP ↓ 7–10 mm Hg and DBP ↓ 5–7 mm Hg in the training group (range of change values).	A number of these subjects exercised an additional 6-mo and saw no further change.

TABLE 4. Effect of age on the magnitude of change in triglycerides and HDL-cholesterol consequent to exercise training.

Study, Country	Study Design and Population	Training Program	Results	Comments
Adolescents				
Tolfrey et al., 2000 (48) UK	Review article summarizing lipid and lipoprotein changes with aerobic exercise training from 14 published studies. The number of experimental subjects/study varied from 8 to 41 and the age from 6 to 18 yr.	All studies used aerobic exercise with study durations of 2.5–52 wk. No other details were provided.	The results of the analyses suggest that aerobic training has little or no effect on lipids and lipoproteins, although studies of longer duration tended to demonstrate more positive results, i.e., improved lipid profile.	The authors conclude that the cross-sectional studies in children, comparing "trained" vs "untrained" groups, tend to mirror cross-sectional studies in adults, i.e., more favorable lipid profiles for "trained" groups. Note: these training studies in children and adolescents tend to "mirror" training studies in adults.
Young and Middle-Aged Adults				
Lokey and Tran, 1989 (32) USA	A meta-analysis was conducted on a total of 27 training studies in which women were subjects and where lipids and lipoproteins were the main outcome variables.	There was a total of 460 women subjects, 379 experimentals, and 81 controls, with a mean age of 29.5 yr. Aerobic exercise was used in 26 of the studies and circuit weight training in one study. The average training period was 12 wk. No additional information on the training programs was provided.	No data were presented on changes in fitness levels. TG ↓ 8.8 $mg \cdot dL^{-1}$ (from 91.2 to 82.4 $mg \cdot dL^{-1}$) and HDL-C ↑ 1.5 $mg \cdot dL^{-1}$, but the change in HDL-C was not statistically significant. The ratio of total cholesterol to HDL-C ↓ significantly.	The authors reported that those women most at risk for heart disease responded most favorably to exercise training.
Tran et al., 1983 (51) USA	A meta-analysis was conducted on a total of 66 training studies conducted on men and women in whom lipids and lipoproteins were the main outcome variables.	There was a total of 2925 subjects (2086 experimentals and 839 controls; 2498 men (85%) and 427 women) with a mean age of 35 yr. Exercise program characteristics were not provided but were used in correlational analyses.	No data were presented on changes in fitness levels. TG ↓ by 15.8 $mg \cdot dL^{-1}$ and HDL-C ↑ by 1.2 $mg \cdot dL^{-1}$, but the change in HDL-C was not statistically significant. The ratio of total cholesterol to HDL-C ↓ significantly.	The lack of detail on the exercise program characteristics makes it difficult to interpret these findings. It was reported that the changes in lipids and lipoproteins were strongly correlated with their initial levels. Larger ↓ in TG and ↑ in HDL-C occurred in the older subjects.
Tran and Weltman, 1985 (50) USA	A meta-analysis was conducted on a total of 95 training studies conducted on men and women in whom lipids and lipoproteins were the main outcome variables. Data were partitioned into three groups depending on whether the subjects gained weight, lost weight, or their weight remained the same.	No details were provided on the number of subjects or on the composition and characteristics of the subject population. No details were provided concerning the exercise training programs used in these studies.	No data were presented on changes in fitness levels. In the group that did not lose body weight, TG ↓ 14.0 $mg \cdot dL^{-1}$ (from 128.1 to 114.1 $mg \cdot dL^{-1}$) and HDL-C ↑ 1.7 $mg \cdot dL^{-1}$ (from 51.8 to 53.5 $mg \cdot dL^{-1}$). The ratio of total cholesterol to HDL-C ↓ significantly.	Age, sex, and quality of the experimental design were found to be unrelated to the study outcomes.
Older and Elderly Adults				
Motoyama et al., 1995 (34) Japan	Elderly men (N = 14) and women (N = 16), 63–85 yr of age, were randomly divided into exercise and control groups, each group composed of 7 men and 8 women.	The exercise group walked on a treadmill for 30 $min \cdot d^{-1}$, 3–6 $d \cdot wk^{-1}$, at an intensity equivalent to individually assessed lactate threshold (LT), or ~50% $\dot{V}O_{2max}$, for a period of 9 mo. The subjects were followed for an additional month of detraining.	There was a 10.5% ↑ in the treadmill speed at LT for the exercise group. HDL-C ↑ by 18.6% in the exercise group, but remained unchanged in the control group. TG appeared to ↓ (12.9%), but this was not statistically significant and was matched by a similar ↓ in the control group (−8.4%). HDL-C ↓ during the month of detraining.	The results were not presented independently by sex.
Seals et al., 1984 (43) USA	Healthy men and women volunteered to participate in this study; 11 in the exercise group (age, 63 ± 1 yr) and 10 in the control group (age, 63 ± 2 yr).	Exercising subjects trained for 6 mo at low intensity (LI; at least 3 $d \cdot wk^{-1}$ for ~30 $min \cdot d^{-1}$, at 60% HR_{max}) and for 6 mo at high intensity (HI; at least 3 $d \cdot wk^{-1}$, 30–45 $min \cdot d^{-1}$, at 80–90% of HR_{max}).	$\dot{V}O_{2max}$ ↑ 12% during the first 6 mo of LI training, and an additional 18% after 6 mo of HI training. TG and HDL-C remained unchanged after LI, but TG ↓ 21% and HDL-C ↑ 14% following HI.	Either or both duration and intensity had a significant effect on the response of the lipids and lipoproteins.
Prepubescents vs Adults				
Savage et al., 1986 (39) USA	Prepubescent boys (N = 34; age, 8.5 yr) and adult men (N = 34; age, 36 yr) were randomly assigned to low-intensity (L; 40% $\dot{V}O_{2max}$), high-intensity (H; 75% $\dot{V}O_{2max}$), and control groups.	Exercising subjects trained 3 $d \cdot wk^{-1}$ for 10 wk, building to a duration necessary to cover 4.8 $km \cdot d^{-1}$.	$\dot{V}O_{2max}$ ↑ by 4.6% and 2.7% in the L groups and by 4.7% and 7.9% in the H groups for boys and men, respectively (only changes in H groups were significant). HDL-C ↓ in all exercise groups, and TG remained unchanged.	There were no differences between prepubescent boys and men in their changes in aerobic capacity or in serum lipids and lipoproteins.

TABLE 4. *Continued*

Study, Country	Study Design and Population	Training Program	Results	Comments
Young Adult vs Older Adult				
Giada et al., 1995 (14) Italy	A group of young male cyclists (YC; N = 12; age, 24 ± 6 yr) and a group of older male cyclists (OC; N = 12; age, 55 ± 5 yr) and an equal number of young and older untrained controls, matched for age, height, and weight, were recruited to participate in this study.	The two groups of cyclists were evaluated in the trained state and following a 2-mo period of detraining.	$\dot{V}O_{2max}$ ↓ by 17% (YC) and 16% (OC) in the two groups of cyclists after detraining. TG ↑ by 15% (Y) and 22% (O) following detraining, while HDL-C ↓ by 10% (YC) and 9% (OC).	The authors concluded that age did not significantly influence the changes in plasma lipids in response to deconditioning, although statistical confirmation of this was not provided.
Leon et al., 2000 (29) USA	The HERITAGE Family Study: Volunteers (N = 675) included black and white men and women, 17–65 years of age. No control group was used.	Trained 3 d·wk^{-1} for a total of 60 exercise sessions on cycle ergometers, starting at 55% of $\dot{V}O_{2max}$ for 30 min per session and building to 75% of $\dot{V}O_{2max}$ for 50 min per session for the last 6 wk.	$\dot{V}O_{2max}$ ↑ by 15.1% in men and 18.6% in women. TG ↓ significantly only during the first 24 h after training suggesting an acute effect of the last exercise bout. HDL-C ↑ significantly.	Analyses of these data demonstrated no significant effect of age on the training response.
Schwartz, 1988 (41) USA	A group of young men (Y; N = 18; age, 31.9 ± 5.5 yr) and a group of older men (O; N = 10; age, 65.1 ± 6.1 yr) were recruited to participate in this study. There was no control group.	Subjects trained 3 d·wk^{-1}, walking and/or jogging, working up to 40 min·d^{-1} at an intensity of 80–85% of maximum heart rate reserve, for a total of 3 mo. After the first 2–4 wk, subjects were given exercises to do at home an additional 2 d·wk^{-1}. The home exercises were not specified.	$\dot{V}O_{2max}$ ↑ by 18% (Y) and 10% (O) ($P < 0.05$). There were no significant differences between Y and O in the changes in TG after training, although the ↓ in TG for O was statistically significant while the change for Y was not. Both groups ↑ HDL-C, although the ↑ in only the Y group was statistically significant.	The older subjects progressed more slowly with respect to the intensity and duration of exercise. Overall, there were no statistically significant differences in the changes experienced by the two groups.
Schwartz et al., 1992 (42) USA	A group of young men (Y; N = 12; age, 28.2 ± 2.4 yr) and a group of older men (O; N = 15; age, 67.5 ± 5.8 yr) were recruited to participate in this study. There was no control group.	Subjects trained 5 d·wk^{-1}, walking, jogging, and/or cycling, gradually increasing duration and intensity up to 45 min·d^{-1} at 85% of maximal heart rate reserve for a total of 6 mo.	$\dot{V}O_{2max}$ ↑ by 18% (Y) and 22% (O). HDL-C ↑ 14% in the Y and 15% in the O (no difference between groups) and TG ↓ only in the O group by 21%.	The difference in the response of TG to training was eliminated when the data were corrected for initial TG levels and the change in BMI.

hypertensives and −10/−8 in hypertensives. Subsequent individual studies would support these estimates, although one meta-analysis did not support a difference by health status (19) (Evidence Category B).

Blood Lipids and Lipoproteins

Effect of age. Table 4 presents the available data on the blood lipid and lipoprotein responses to exercise training as affected by age. Not all studies reported significant favorable changes in either or both TG and HDL-C with training. However, the majority of the studies did report significant changes. In those studies where direct comparisons were made across age groups, no significant differences in responses were reported. Thus, age does not appear to affect the response to training. The magnitude of change in TG and HDL-C was quite variable, with the HDL-C changes generally being small on average (i.e., <3 mg·dL^{-1}) (Evidence Category B).

Effect of sex. Table 5 presents the available data on the blood lipid and lipoprotein responses to exercise training as affected by sex. Although not all studies reported favorable changes in TG and HDL-C, the majority did. There was not a consistent pattern of response differentiating males and females. Although a number of studies reported no difference in response between males and females when there was a significant change, about an equal number reported more favorable changes in HDL-C in males, with only one study showing a more favorable change in females. With TG, where there were differences in response between males and females, the studies were split, with three showing a greater decrease for females and three showing a greater decrease for males. Many of the studies reported the ratio of total cholesterol (TC) to HDL-C (TC/HDL-C ratio), and there were no apparent consistent differences between men and women in their improvement in this ratio (i.e., decreased TC/HDL-C ratio) (Evidence Category B).

Effect of health status. Table 6 presents the available data on the blood lipid and lipoprotein responses to exercise training as affected by health status. For this analysis, because of the large number of training studies on post-MI patients and the lack of training studies comparing post-MI patients with healthy, age-matched controls, the data from three meta-analysis studies are presented. From these studies, it appears that

TABLE 5. Effect of sex on the magnitude of change in triglycerides and HDL-cholesterol consequent to exercise training.

Study, Country	Study Design and Population	Training Program	Results	Comments
Prepubertal and Adolescents				
Sasaki et al., 1987 (38) Japan	Obese boys (N = 21) and girls (N = 20), 11 yr of age, volunteered to participate in this study. Nonobese boys and girls served as controls.	All subjects ran 20 min·d^{-1}, 7 d·wk^{-1} for 2 yr at their individually determined lactate thresholds.	Estimated $\dot{V}O_{2max}$ ↑ by 14.5%. HDL-C ↑ significantly in both boys (16%) and girls (19%) by the end of the first year and then ↓ slightly during the second year. TG ↓ by the end of the second year, but only in girls.	The subjects in the experimental groups did not diet, yet their weight gain was significantly attenuated when compared to controls.
Tolfrey et al., 1998 (47) England	Prepubertal children (N = 48; age, 10.6 yr) were recruited to participate in this study. There were 14 boys and 14 girls in the exercise groups and 10 boys and 10 girls in the control groups. The groups were not randomized, but were maturity-matched.	Exercising subjects trained on cycle ergometers 30 min·d^{-1}, 3 d·wk^{-1} for 12 wk, at 80% of HR_{peak}. Controls maintained their usual pattern of activity.	$\dot{V}O_{2max}$ ↑ by 4.9% when expressed in mL·kg$^{0.66}$·min^{-1}. TG did not change, but HDL-C ↑ by 9.3% in the exercise group and ↓ by 8.9% in the control group.	There were no differences in response between boys and girls (personal communication with Dr. Tolfrey on September 4, 2000).
Young and Middle-Aged Adults				
Blumenthal et al., 1991 (2) USA	Pre- (PreM; N = 25; age, 42) and postmenopausal (postM; N = 25; age 47 yr) women, 45–57 yr of age, were randomly assigned to 12-wk of either aerobic (walking and jogging) or nonaerobic exercise (resistance training). There were no nonexercising control groups.	Aerobic group (A) trained 3 d·wk^{-1} for 50 min (15-min warm-up and 35-min aerobic exercise) at 70% of maximal HR reserve. Resistance group (R) trained 2 d·wk^{-1} for 55 min (20 min stretching and 35 min circuit training).	$\dot{V}O_{2max}$ ↑ by 17.8% in preM and 16.6% in postM, with no change in the R groups. Strength changes were not reported. HDL-C and TG were unchanged in all four groups.	There were no differences in the changes in aerobic capacity or lipid levels between preM and postM groups.
Brownell et al., 1982 (4) USA	Healthy men (N = 24; age, 42 yr) and women (N = 37; age, 35 yr) volunteered to participate in this study. There was no nonexercising control group.	Subjects exercised 15–25 min·d^{-1}, 3 d·wk^{-1}, at an intensity of 70% HR_{max}, for a total of 10 wk.	Estimated $\dot{V}O_{2max}$ ↑ 10.2% in men and 8.9% in women. HDL-C did not change in either group, although women showed a trend to ↓ and men to ↑. TG was significantly ↓ in men, but there was a trend to ↑ in women.	
Farrell and Barboriak 1980 (11) USA	Men (N = 7; age, 22.3 ± 1.7 yr) and women (N = 9); age 23.6 ± 3.9 yr) volunteered to participate in this study. There was no control group. Lipids and lipoproteins were measured every 2 wk.	All subjects ran at ~70% $\dot{V}O_{2max}$ for ~30 min·d^{-1}, 3–4 d·wk^{-1} for a total of 8 wk.	$\dot{V}O_{2max}$ ↑ 8.8% in men and 9.7% in women. HDL-C ↑ and TG ↓ significantly over the 8-wk period, with men and women having similar patterns of change.	This study shows that the incremental changes over 2-wk periods were nearly identical in men and women.
Goldberg et al., 1984 (16) USA	Men (N = 6; age, 33 yr) and women (N = 8; age, 27 yr) volunteered to participate in this study. There was no control group.	All subjects participated in a progressive resistance training program for 16 wk, exercising 3 d·wk^{-1}, 45–60 min·d^{-1}.	Strength performance ↑ 260% in women and 147% in men. Women ↑ HDL-C by 4.8% (NS) and ↓ TG by 28.3%, where men ↑ HDL-C by 15.8% (NS) and TG did not change.	This study supports the role of resistance training in altering lipids and lipoproteins and shows a different pattern of change for men and women, although the HDL-C changes were NS.
Hill et al., 1989 (22) USA	Men (N = 8) and women (N = 9), 22–45 yr of age, volunteered to participate in this study. There was no control group.	All subjects participated in aerobic activities (usually walking and jogging) at an intensity of 70% of HR_{max}. They started exercising for 20 min, 3 d·wk^{-1} and increased to 60 min, 4 d·wk^{-1} for 10 wk.	$\dot{V}O_{2max}$ ↑ 18% in men and 13% in women. HDL-C ↑ in women by 11%, but did not change in men. Total cholesterol (TC) ↓ in men, but not in women, thus there were no sex differences in the ↑ in the HDL/TC ratio.	TG were not measured in this study.
Juneau et al., 1987 (25) USA	A total of 60 health men (age, 49 ± 6 yr) and 60 health women (age, 47 ± 5 yr) volunteered for this study. Subjects were randomized to exercise and control groups by sex (N = 30/group).	The exercise groups participated in a 6-mo home-based program, walking or jogging 5 d·wk^{-1} for a duration equal to an energy expenditure of 4 kcal·kg^{-1} (average of 47 min for men and 54 min for women), at 65% to 77% of HR_{max}.	$\dot{V}O_{2max}$ ↑ 15% in men and 9% in women (> ↑ in men associated with greater adherence). No significant changes were noted in HDL-C or TG for either men or women.	There were trends for an ↑ in HDL-C and a ↓ in TG for both men and women, but these were not statistically significant.
King et al., 1991 (28) USA	Random assignment to one of four groups: higher intensity group-based training (HI-G); higher intensity home-based training (HI-H); lower intensity home-based (LI-H); and control. Men (N = 197) and women (N = 160), 50–65 yrs old, sedentary and free of CVD.	HI training groups exercised 3 d·wk^{-1}, 40 min·d^{-1}, at 73–88% of peak treadmill heart rate for a period of 12 mo; LI training group exercised 5 d·wk^{-1}, 30 min·d^{-1}, at 60–73% of peak treadmill heart rate.	$\dot{V}O_{2max}$ ↑ by 5.9% and 2.5% (HI-G); 4.0% and 6.1% (HI-H); and 4.6% and 4.0% (LI-H) for men and women, respectively. No significant changes were found in either TG or HDL-C at 6 or 12 mo in the exercise groups compared to the control groups.	There were no reported sex differences in response.

TABLE 5. *Continued*

Study, Country	Study Design and Population	Training Program	Results	Comments
Leon et al., 2000 (29) USA	(See Table 4 for details)	(See Table 4 for details)	$\dot{V}O_{2max}$ ↑ by 15.1% in men and 18.6% in women. TG ↓ significantly posttraining in men, but not women. HDL-C ↑ significantly in both men and women.	The lack of change in TG after training was the only sex-related difference in results.
Lipson et al., 1980 (31) USA	Young men (N = 5) and women (N = 5), 19–22 yr of age, volunteered to participate in this study. There was no control group.	All subjects walked or jogged on a treadmill 30 min·d^{-1} at 70% of $\dot{V}O_{2max}$ for 6 wk (frequency, d·wk^{-1}, was not specified).	$\dot{V}O_{2max}$ ↑ 8.2% for men and 14.4% for women. HDL-C and TG appeared to ↓ in both men and women, but the changes were not statistically significant.	Differences in response by sex were not analyzed. However, since the overall changes were not statistically significant, is it likely that there were no significant differences between men and women.
Lokey and Tran, 1989 (32) USA	(See Table 4 for details)	(See Table 4 for details)	No data were presented on changes in fitness levels. TG ↓ 8.8 mg·dL^{-1} (from 91.2 to 82.4 mg·dL^{-1}) and HDL-C ↑ 1.5 mg·dL^{-1}, but the change in HDL-C was not statistically significant. The ratio of total cholesterol to HDL-C ↓ significantly.	The authors reported that the changes for both TG and HDL-C were less in women compared with men.
Stefanick et al., 1998 (46) USA	Postmenopausal women, 45–64 yr (N = 180), and men, 30–64 yr (N = 197), were recruited to participate in this study. Subjects were healthy but had low HDL-C and high LDL-C levels. They were randomly assigned to one of four groups: control, exercise, NCEP Step 2 diet, or exercise + diet.	The exercise program for this 1-yr study consisted of brisk walking or jogging, 60 min·d^{-1}, 3 d·wk^{-1} for the first 6 wk, and 16 km of brisk walking or jogging per week for the remainder of the program. Exercise intensity was not specified.	Men and women in both exercise groups significantly ↑ $\dot{V}O_{2max}$ as compared with the control and diet-only groups, with no difference by sex. TG values remained unchanged in all groups. The changes in HDL-C in the two exercise groups were not significant when compared to the control and diet-only groups.	There was a trend for the HDL-C to ↓ in women in the diet + exercise group.
Vasankari et al., 1998 (52) Finland	A total of 104 previously sedentary men (N = 34; age, 43.6 ± 5.3 yr) and women (N = 70; age, 44.6 ± 6.7 yr) volunteered to participate in this study.	The specifics of the exercise program were not defined. It appears that subjects exercised at home and kept logs of what they did, reporting to supervised sessions 3 d·mo^{-1}. The duration of the exercise program was 10 mo.	Estimated $\dot{V}O_{2max}$ ↑ 19% in both men and women. HDL-C ↑ 15% in men and 5% in women. TG did not change in either men or women.	The lack of detail regarding the exercise prescription makes it difficult to interpret the results of this study.
Warner et al., 1995 (53) USA	Patients in an outpatient cardiac rehabilitation program were followed over a 5-yr period. The subjects included 553 men (57.2 yr) and 166 women (58.9 yr).	The patients exercised 3 d·wk^{-1} for 10 min of stretching and 30–40 min of walking, jogging or stationary cycling at 70–85% of HR_{max}.	Aerobic capacity changes were not presented. HDL-C ↑ in a similar manner in men and women at the end of the first year, but at the end of 5 yr, women ↑ by 20% and men by only 5%. TG ↓ equally in both groups.	The 5-yr data demonstrated a major sex difference in HDL-C that was not present at the end of 1 yr.
Woolf-May et al., 1998 (58) UK	A total of 62 subjects volunteered for this study, 31 men and 31 women, 40–71 yr. They were randomly assigned to one of three groups: long walkers (LW; 11 men and 11 women); repetitive short walkers (SW; 9 men and 14 women); and controls (11 men and 6 women).	Both exercise groups performed an 18-wk walking program. LW were asked to walk at least 20 min, but not more than 40 min, once per day, and the SW were to walk for at least 10 min, but not more than 15 min, per session and to not complete more than three sessions per day. Both groups were to walk 60 min the first week and to build to 200 min·wk^{-1} by the 12th wk. Intensity was set at 70–75% of estimated $\dot{V}O_{2max}$ in both groups.	$\dot{V}O_{2max}$ was not measured, but peak HR achieved during a step test ↓ by 4.3% and 4.9% in long and short walkers, respectively. Neither TG or HDL-C were changed after training in any of the groups. There were no differences in response by sex.	The authors attribute the lack of significant changes in this population of subjects to their favorable lipid and lipoprotein levels before intervention.
Woolf-May et al., 1999 (59) UK	A total of 79 subjects volunteered and were cleared for participation in this study, 25 men and 54 women, 40–66 yr. They were randomly assigned to one of four groups: long walkers (LW); intermediate walkers (IW); short walkers (SW); and controls. Fifty-six subjects completed the study.	Both exercise groups performed an 18-wk walking program. The LW were to walk at least 20 min, but not more than 40 min, once per day; the IW were to walk at least 10 min, but no more than 15 min, per session, with not more than three sessions per day; and the SW were to walk for at least 5 min, but not more than 10 min, per session and to not complete more than four sessions per day. All groups were to walk 60 min the first week and to build to 200 min·wk^{-1} by the 9th wk. Intensity was set at 70–75% of estimated $\dot{V}O_{2max}$ in all groups.	$\dot{V}O_{2max}$ was not measured, but peak HR achieved during the final stage of a graded treadmill walking test ↓ (NS) as did peak lactate ($P < 0.001$). Neither TG or HDL-C was changed after training in any of the exercise groups. There were no differences in response by sex.	Several other lipid-lipoprotein variables did change significantly and in a favorable direction, but they did not differ by sex.

TABLE 5. *Continued*

Study, Country	Study Design and Population	Training Program	Results	Comments
Woolf-May et al., 2000 (57) UK	Men (N = 37, age, 57 ± 7 yr) and women (N = 60; age, 54 ± 7 yr) were randomly assigned to groups of walkers or controls.	The exercise groups walked 60 min·wk^{-1} the first week increasing to 200 min·wk^{-1} by the 13th wk, at an intensity of 75–80% of predicted HR_{max} for a total of 18 wk.	$\dot{V}O_{2max}$ changes were not reported. There were no changes in TG or HDL-C consequent to training.	Women had a better lipid profile before training, but there were no sex differences in response to training.
Wood et al., 1991 (56) USA	Random assignment of moderately overweight men (N = 132) and women (N = 132), 25–49 yr of age, to one of three groups: control; hypocaloric NCEP diet; hypocaloric NCEP diet + exercise. Subjects were previously sedentary and free of CVD.	The diet + exercise group performed brisk walking and jogging 3 d·wk^{-1}, building to at least 45 min·d^{-1}, at an intensity of 60–80% of HR_{max} for a period of 12 mo.	$\dot{V}O_{2max}$ ↑ by 25.2% in men and 23.7% in women. TG ↓ and HDL-C ↑ in men who exercised and dieted compared to both diet-only and control groups. In women who exercised and dieted, TG ↓ compared to the control group, but not the diet-only group. HDL-C was significantly ↑ when compared to the diet-only group.	Despite the large weight loss associated with the diet of 4–5 kg in the intervention groups, exercise appeared to have an independent effect on HDL-C in both men and women. Exercising women maintained their HDL-C levels, while men increased theirs. Diet-only women ↓ their HLD-C levels while men maintained theirs.
Older and Elderly Adults				
Cauley et al., 1987 (5) USA	Postmenopausal women were randomized into walking (N = 100; age, 58 ± 4) or control (N = 104; age, 57 ± 4) groups.	Subjects in the walking group were to achieve and maintain a walking program of 7 miles·wk^{-1} for a period of 2 yr.	Physical activity increased in the walking group, but no measures of fitness were reported. There were no changes in HDL-C or TG.	While activity levels increased considerably over 2 yr, this did not translate into changes in lipids and lipoproteins.
Hughes et al., 1994 (23) USA	Healthy men and women (N = 39; 50–78 yr) with impaired glucose tolerance were sequentially assigned to one of three 12-wk interventions: exercise training (2 groups); low-fat diet; and exercise training + low-fat diet.	The program for the two exercise-only groups included aerobic exercise 4 d·wk^{-1} for 45 min·d^{-1} at 75% of maximum heart rate reserve (HRR) for N = 8 and 50% HRR for N = 9. Those in the exercise + diet group (N = 10) exercised at 75% of HRR.	$\dot{V}O_{2max}$ ↑ in all exercise groups but the changes were not reported. Exercise alone did not affect either TG or HDL-C concentrations. HDL-C ↓ in exercise training + diet group, while TG remained unchanged.	It should be noted that these were "healthy" subjects, yet they had impaired glucose tolerance.
Joseph et al., 1999 (24) USA	Men (N = 18) and women (N = 17), 54–71 yr, volunteered to participate in this study. There was no control group.	All subjects resistance trained 2 d·wk^{-1} for a period of 12 wk using progressive resistance training procedures.	Total body strength ↑ in both men (19%) and women (23%). HDL-C ↑ by 5.6% in men and ↓ by 6.2% in women. TG remained unchanged in both groups.	There was a trend for TG to ↓ in men and ↑ in women.
Schuit et al., 1998 (40) Netherlands	A group of 229 eligible subjects, 60–80 yr, were randomly assigned to one of three groups: cycle ergometer (48 men and 48 women), all-around activity (25 men and 22 women) and control (40 men and 46 women).	Cycle ergometer group trained at home 4 d·wk^{-1}, 30 min·d^{-1} at a HR corresponding to 70% of their peak work rate, for 6 mo. The all-around activity group met 3 d·wk^{-1}, 45 min·d^{-1}, for 6 mo using aerobic exercise games, exercise to music, calisthenics, and flexibility exercises.	Peak power output ↑ 10.7% in the cycle group and 6.6% in the all-around group. There was no change in the control group. TG ↓ in the women in the two exercise groups. HDL-C remained unchanged in the cycle group and ↓ in the all-around group.	HDL-C did ↑ in the cycle and control groups, but ↓ in the all-around group. No sex-specific changes were noted for HDL-C.

somewhat larger decreases in TG and increases in HDL-C occur in the post-MI patient population, which is likely related to their higher pretraining levels for TG and lower levels for HDL-C (Evidence Category B).

DISCUSSION

It is important to recognize that there are a number of factors that influence the training response results of those studies that have been presented in this review, in both the areas of blood pressure and blood lipids and lipoproteins. In both areas, it appears that greater changes are possible for those subjects starting with a less favorable profile, i.e., higher SBP and DBP, higher TG, and lower HDL-C. This has been a major finding of most reviews and meta-analyses. Since men typically have higher SBP, DBP, and TG, and lower HDL-C when compared with women, men would be expected to have a greater change in these variables with training, which was, for the most part, the conclusion of this article. However, this was not the case with age, where very few studies supported differences across age in response to training for blood pressure and for blood lipids and lipoproteins, even though older individuals tend to have more unfavorable profiles.

Another confounding variable is body size. It has been well established that blood pressure is a function of body size in children and animals, and is likely a factor in full-grown adults. Yet, blood pressure is generally reported as an absolute value, without adjusting for body size. Thus, men are likely to have higher blood pressure values solely on the basis of their larger body size on average. How this might affect the response to training is less clear. Another variable that can affect the results of training studies is plasma volume. Blood lipid and lipoprotein values are reported as concentrations, yet few

TABLE 6. Effect of health status (CVD vs no CVD) on the magnitude of change in triglycerides and HDL-cholesterol consequent to exercise training.

Study, Country	Study Design and Population	Training Program	Results	Comments
Lokey and Tran, 1989 (32) USA	A meta-analysis was conducted on a total of 27 training studies in which women were subjects and where lipids and lipoproteins were the main outcome variables.	(See Table 4 for details)	(See Table 4 for details)	The authors reported that those women most at risk for heart disease responded most favorably to exercise training.
Tran and Brammell 1989 (49) USA	A meta-analysis was conducted on a total of 15 studies published between 1976 and 1984, in which subjects were post-MI patients and where lipids and lipoproteins were the main outcome variables.	A total of 526 male post-MI patients, with an average age of 52.6 ± 4.9 yr, were included as subjects. They trained an average of 25.1 wk at an average intensity of 74.4% of HR_{max}, an average of 4.1 $d \cdot wk^{-1}$ for an average of 45.6 $min \cdot d^{-1}$.	Changes in fitness levels with training were not reported. TG ↓ 20 $mg \cdot dL^{-1}$, from 169 to 149 $mg \cdot dL^{-1}$ and HDL-C ↑ 4 $mg \cdot dL^{-1}$, from 41 $mg \cdot dL^{-1}$ to 45 $mg \cdot dL^{-1}$. The ratio of total cholesterol to HDL-C ↓ from 5.7 to 5.0.	The changes in TG were significantly correlated to changes in body weight (r = 0.60), but this was not the case for HDL-C.
Tran et al., 1983 (51) USA	A meta-analysis was conducted on a total of 66 training studies conducted on men and women in whom lipids and lipoproteins were the main outcome variables.	There was a total of 2925 subjects (2086 experimentals and 839 controls; 2498 men (85%) and 427 women) with a mean age of 35 yr. Exercise program characteristics were not provided but were used in correlational analyses.	No data were presented on changes in fitness levels. TG ↓ by 15.8 $mg \cdot dL^{-1}$ and HDL-C ↑ by 1.2 $mg \cdot dL^{-1}$, but the change in HDL-C was not statistically significant. The ratio of total cholesterol to HDL-C ↓ significantly. Pre- and posttraining data were not provided.	The lack of detail on the exercise program characteristics makes it difficult to interpret these findings. It was reported that the changes in lipids and lipoproteins were strongly correlated with their initial levels. Larger ↓ in TG and ↑ in HDL-C occurred in the older subjects.

studies have adjusted for the changes in plasma volume, both acute and chronic, that occur in response to training.

Future research in this area should focus on developing research designs that actually investigate the influence of age, sex, and health status on the blood pressure and blood lipid and lipoprotein responses to exercise training. Subjects should be randomized into exercise and control groups by age, sex, or health status depending on the purpose of the study. Furthermore, power analyses should be conducted to ensure an adequate number of subjects in each group, and repeat measures should be taken both before and after training to increase the accuracy of measurement for the outcome variables. Few studies that have been reported in this review met all of these criteria. The changes in these variables have typically been small. Furthermore, in the HERITAGE Family Study, intraclass correlations for repeat measures of resting SBP and DBP before training ranged from 0.76 to 0.85, technical errors were 5.1 mm Hg or less, and coefficients of variation were less than 7% (45). This emphasizes the importance of having repeat measures in order to determine small differences between subgroups where the magnitude of change is small.

In summary, it is concluded that age has little or no influence on the changes in blood pressure or in blood lipids and lipoproteins (TG and HDL-C) in response to exercise training. When looking at sex, females appear to have an attenuated response to exercise training compared with males with respect to SBP, DBP, and HDL-C, but the data for TG are equivocal. Finally, there appears to be more favorable changes in resting SBP and DBP, TG, and HDL-C in unhealthy subjects (hypertensive and post-MI patients) when compared with healthy subjects.

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Population attributable risk: implications of physical activity dose

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ABSTRACT

MACERA, C. A., and K. E. POWELL. Population attributable risk: implications of physical activity dose. *Med. Sci. Sports Exerc.,* Vol. 33, No. 6, Suppl., 2001, pp. S635–S639. **Purpose:** The purpose of this study is to describe the application of population attributable risk estimates in relation to the dose-related benefits or risks of physical activity. **Methods:** Assumptions and limitations of population attributable risk calculations and interpretations are reviewed and evaluated in the context of physical activity dose. Theoretical estimates are developed for several hypothetical situations. **Results:** National estimates of population attributable risk may be inaccurate because definitions and measurement techniques applied in physical activity research studies and physical activity prevalence surveys do not correspond. In addition, it is not established whether vigorous or moderate physical activity are independent contributors, sequential categories, or interactive variables in the process of disease reduction. This information is necessary to calculate population attributable risk most appropriately. **Conclusion:** Estimates of the disease burden of physical inactivity will be improved by two advances in empirical studies: first, the pairing of prevalence and relative risk estimates for nationally representative population-based samples; and second, refined relative risk estimates for various doses of physical activity. **Key Words:** ATTRIBUTABLE RISK, EPIDEMIOLOGIC METHODS, EXERCISE, PHYSICAL ACTIVITY, PREVALENCE, RELATIVE RISK

In epidemiology, relative risk (RR) and similar measures are used to assess the strength of a relationship between a particular exposure and the incidence of a particular disease (or outcome), thus establishing causality and magnitude of risk of exposed individuals compared with unexposed individuals. The public health or societal impact of an exposure, however, depends not only on the magnitude of the relative risk but on the prevalence of the risk factor in the population. Population attributable risk (PAR) can be calculated from estimates of the RR and the population prevalence of the risk factor to provide an estimate of how much of a particular disease could be prevented if exposure to the risk factor were eliminated (1,11,13). A measure such as PAR takes into account both the strength of the association (RR associated with the exposure) and the prevalence of the exposure. Using this approach, the effect of eliminating various risk factors can be compared. For example, PAR estimates have been used to identify physical inactivity as one of the most important modifiable risk factors for coronary heart disease (CHD) (1). Because PAR is a useful tool in assessing the consequences of modifying the prevalence of risky exposures, this article explores how PAR could be used in conjunction with varying doses of physical activity and details some of the problems inherent in its interpretation. For simplicity, CHD will be the only outcome used in the following examples. The estimates presented here are derived from currently available data and will naturally change as new information emerges.

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ASSUMPTIONS

PAR is calculated by using the prevalence (P) of a risk factor and the RR of that risk factor with a particular outcome (PAR = (P*(RR − 1))/(P*(RR − 1) + 1)). It is often expressed as a percentage by multiplying by 100. PAR is a theoretical calculation rather than an empirical assessment of the effect of modifying a particular risk factor. Although useful from both conceptual and pragmatic perspectives, PAR has important limitations. A discussion of these limitations will assist in the overall interpretation of the measure. We describe six categories of limitations: 1) PAR is a useful but imaginary concept; 2) independently calculated PARs of different risk factors for the same outcome cannot be added; 3) PAR assumes that known and unknown risk factors are randomly distributed in the population; 4) RR, and therefore PAR, may differ for disease incidence, morbidity, and mortality; 5) physical activity has been measured and categorized differently in general population surveys and in observational studies of relative risk; and 6) different effects of vigorous and moderate activity on health outcomes have not been sufficiently clarified to know the most appropriate manner by which to incorporate them into calculations of PAR.

PAR is a useful but imaginary concept. It predicts health outcomes in an imaginary world in which people change their physical activity level and nothing else. The prevalence of other behaviors and risk factors such as blood pressure and blood cholesterol remain constant in PAR

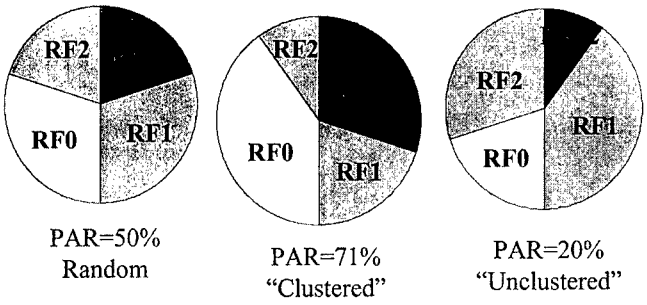


FIGURE 1—Population attributable risk percentages for Risk Factor 1 (RF1) with different distributions of Risk Factor 1 and Risk Factor 2 (RF2). In all cases, prevalence of RF1 = 50% and RF2 = 40%. RR for RF1 = 3, RF2 = 6, and RF12 = 18.

calculations. To the extent the prevalence of these risk factors is expected to change as activity changes, PAR underestimates probable changes in health outcomes.

Independently calculated PARs of different risk factors for the same outcome cannot be added. As just noted, independent calculations of PAR assume that nothing else changes. Although we know that most chronic diseases have multiple causes and can be affected by several risk situations, PAR evaluates one risk factor at a time and the calculation assumes that the prevalences of the other risk factors are held constant. When information is available for several risk factors (e.g., smoking, physical inactivity, high blood pressure, high serum cholesterol as related to CHD), separate PAR estimates can be calculated for each, but these estimates cannot be added together. For example, summing the PAR estimates for physical inactivity and for high blood pressure will overestimate the effect on CHD when both physical inactivity and high blood pressure were removed simultaneously. The PAR estimate for each risk factor can be evaluated separately and may prove useful for program planning or for comparing potential risk factor interventions, but adding them together gives an inaccurate picture of the combined effect of changing several risk factors at the same time.

PAR assumes other risk factors are randomly distributed in the population. If risk factors are clustered within individuals, PAR is an overestimate. If risk factors are unclustered within individuals, PAR is an underestimate. This concept is illustrated in Figure 1 using three pie charts each displaying different distributions of two risk factors while holding the prevalence and the RR of each risk factor constant (Fig. 1). In this example, the RR for Risk Factor 1 is 3.0; the RR for Risk Factor 2 is 6.0; and the RR for having both risk factors (Risk Factor 12) is 18.0. For each pie in the example, the prevalence of Risk Factor 1 is 50% and the prevalence of Risk Factor 2 is 40%. In this hypothetical situation, the PAR varies for Risk Factor 1 from 20% when the risk factors are not clustered to 71% when they are clustered. The PAR when the risk factors are randomly distributed (the assumed situation) is 50%. Therefore, when interpreting the PAR for a given disease outcome, attention should be given as to how specific risk factors combine or interact to affect the disease process. Because CHD risk factors do cluster within individuals, PAR may overestimate the effect of a single risk factor such as physical inactivity. The extent to which this overestimate would be counterbalanced in reality by changes induced in other risk factors (e.g., if physical activity increases and blood pressure decreases) could be modeled and calculated.

RR, and therefore PAR, may differ for disease incidence, morbidity, and mortality. In the case of CHD, there is sufficient information to suggest that increasing physical activity reduces the risk of developing CHD (incidence), dying from CHD (mortality), and incurring associated disability (morbidity) for persons with CHD. However, the relationship between dose and response may be different for incidence, morbidity, and mortality. The same may be true for other chronic diseases.

Physical activity has been measured and categorized differently in general population surveys and in observational studies of RR. As a result, national PAR estimates are of questionable accuracy because relative risks from specific studies and national physical activity prevalence estimates may not correspond. For a given RR, different prevalence estimates yield different PAR estimates as shown in Figure 2. The larger changes in PAR occur at lower prevalences. Ideally, the RR measures and the population-wide prevalence estimates would come from the same research. Less than ideal, but an improvement over the status quo, would be use of the same physical activity measures and categories in national surveys and in etiologic studies.

The different effects of vigorous and moderate activity on health outcomes have not been sufficiently clarified to know the most appropriate manner by which to incorporate them into calculations of PAR. Vigorous and moderate activity could be considered as independent risk factors (similar to serum cholesterol level and family history of early myocardial infarction), or they could be considered different levels of a continuous or categorical risk factor, or they may be independent but interacting variables (e.g., a set dose of moderate physical activity may have different health effects if spiced

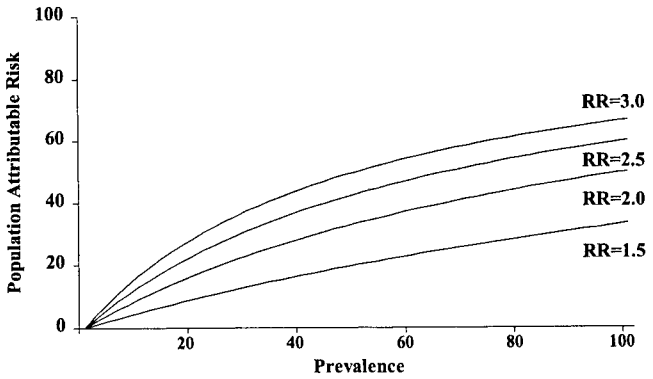


FIGURE 2—Population attributable risk by selected values of relative risk and prevalence.

with a dose of vigorous or hard physical activity). For simplicity, we have assumed a continuous or categorical relationship. The appropriate classification of physical activity intensity remains, however, an important unresolved issue. A closely related issue of special importance for this article is that many of the RR estimates available for various outcomes (CHD, diabetes, obesity), as well as the "best" measures of exposure (e.g., moderate intensity, vigorous intensity), may change as new scientific knowledge emerges. Even using existing information has problems because there is not agreement among studies on the definition of "moderate" or "vigorous" activity, or even "inactivity." Furthermore, many individuals who are classified as doing "moderate" levels of physical activity may actually do both moderate and vigorous activity.

PREVALENCE OF PHYSICAL ACTIVITY IN THE GENERAL POPULATION

Surveillance of physical activity in the United States is conducted annually by the National Center for Health Statistics in the National Health Interview Survey (NHIS) (www.cdc.gov/nchs). Respondents are asked about frequency and duration of self-determined intensities of leisure-time physical activity. These questions are used to track health objectives for "no" leisure-time activity and moderate- or vigorous-intensity activity (www.health.gov/healthypeople). Participation in activities that increase heart rate or breathing are asked, but no examples of specific activities are provided. Those who report no participation in either moderate or vigorous activities are considered "inactive"; those who participate in vigorous activities for at least 20 min on 3 or more $d \cdot wk^{-1}$ are considered "vigorously active"; those who participate in moderate-intensity activities for at least 30 min on 5 or more $d \cdot wk^{-1}$ are considered "moderately active." Another category, "recommended" levels of physical activity, includes those who meet the frequency and duration criteria for either moderate- or vigorous-intensity activity.

The Behavioral Risk Factor Surveillance System (BRFSS) collects state data on physical activity periodically (www.cdc.gov/nccdphp/brfss). Questions used from 1984–2000 ask for a description of the type, duration, and frequency of the respondent's two most common activities in the previous month. Intensity is calculated on the basis of age- and sex-adjusted metabolic expenditure values for each activity (4,9). Comparisons of the 1998 NHIS data and the 1998 BRFSS data are shown in Table 1. As noted in Table 1 and in other publications (2,12,14), the prevalence of physical activity can vary substantially depending on the measurement source, conceptual interpretation of the questions, and cut points or algorithms used to classify physical activity into intensity-related categories on the basis of presumed health effects.

The prevalence estimates of physical activity obtained from surveillance systems may not be appropriate for the calculation of PAR when using RR estimates derived from a specific study population, because the definitions are rarely the same. In these situations, using the prevalence estimates for the various levels of physical activity of the study population itself may provide more accurate PAR estimates.

TABLE 1. Variations in the prevalence of physical activity United States adults, 1998.

Physical Activity Classification	NHIS	BRFSS
Inactive: reporting no leisure-time physical activity	40	29
Insufficient: reporting some activity but not meeting the **Recommended** level	30	44
Recommended: meeting criteria for either **Moderate** or **Vigorous** (below)	29	27
Components of **Recommended** Physical Activity:		
Moderate: reporting ≥5 $d \cdot wk^{-1}$ of moderate-intensity activity ≥30 $min \cdot d^{-1}$	7	13
Vigorous: reporting ≥3 $d \cdot wk^{-1}$ of vigorous-intensity activity ≥20 $min \cdot d^{-1}$	15	6
Reporting both **Moderate and Vigorous:**	7	8

NHIS, National Health Interview Survey; BRFSS, Behavioral Risk Factor Surveillance System.

RELATIVE RISK

In addition to prevalence estimates, the other component of PAR, the RR, is also subject to variation from study to study. A summary of the relationship between physical activity (or inactivity) and the risk of CHD has been reviewed in several publications (10,14) that have generally found that active adults have about half the risk for CHD mortality compared with inactive adults. Included among the identified health benefits of moderate-intensity activity are reduced risk for all-cause mortality or CHD events among those who engage in moderate-intensity activity compared with inactive individuals (3,5). Although it is clear that there is a dose-response relationship between physical activity and CHD, what is not yet known is whether the shape of the dose-response curve is linear or curvilinear. Examples of the range of RR (displayed so that the most active groups are the reference groups) from two studies using different definitions of physical activity are shown in Table 2. In the study of CHD events among female nurses (5), there appears to be a larger difference in the RR between the least active group and the next active group for both total physical activity and for walking without including vigorous activity (quintiles of MET hours per week), suggesting that the nature of the curve is not linear. To a lesser extent, this is also observed in the Lee and Paffenbarger study of all-cause mortality among Harvard Alumni (3).

POPULATION ATTRIBUTABLE RISK

PAR estimates for physical activity and CHD have ranged from 23% to 46%, with the best estimate at around 35% (6). Although these estimates apply to general populations, they are limited because they have usually assumed only two categories of physical activity. Several studies have estimated the PAR of CHD associated with various

intensities and types of physical activity (3,5,7). For example, in the Harvard Alumni cohort, the PAR for sedentary living habits such as not walking at least 9 miles·wk^{-1}, not climbing at least 20 flights of stairs·wk^{-1}, and not participating in a moderately vigorous sports activity were calculated for the entire category (sedentary living) and for each component (7). The PAR (expressed as a percentage) for sedentary living habits was 13.2%. When examining the components of sedentary living, not participating in moderately vigorous sports activity was found to be more important than the others, with a PAR of 12% compared with 9.7% for walking less than 9 miles·wk^{-1} and 8.8% for climbing less than 20 flights of stairs·wk^{-1}. In this analysis, all estimates were adjusted for age as well as for other risk factors for mortality (e.g., cigarette smoking, hypertension, overweight, early parental mortality). Whether using crude or adjusted estimates, the RR and the prevalence estimates for the physical activity categories, as well as the PAR, are specific to this study.

Other studies have created categories of physical activity by calculating volume or total energy expenditure (sometimes combining several intensities) and dividing the groups into quintiles (5) or other using other cut points (3). The RRs for each quintile (or other cut point) are adjusted for other factors, but not necessarily the same factors throughout various studies. Within a particular study the PAR may be useful for comparing the effect of modifying physical activity dose within that study population, but may not be practical for more general use.

TABLE 2. Examples relative risks for physical inactivity from selected epidemiology studies.

Study Population	Outcome	Physical Activity Definition	RR[a]
72,488 female nurses; Manson et al., 1999 (5) (RR adjusted for age only)	Coronary events	Total physical activity score[b]	
		1 (lowest quintile; least active)	2.17
		2	1.67
		3	1.41
		4	1.17
		5 (highest quintile; most active)	1.00
		Walking (no vigorous activity)[a]	
		1 (lowest quintile; least active)	2.17
		2	1.50
		3	1.54
		4	1.13
		5 (highest quintile; most active)	1.00
13,485 men; Harvard Alumni Lee and Paffenbarger, 2000 (3) (RR adjusted for age plus many other factors)	All-cause mortality	Walking	
		<5 km·wk^{-1} (<3.1 miles·wk^{-1})	1.19
		5 to <10	
		10 to <20	1.08
		>20 km·wk^{-1} (>12.5 miles·wk^{-1})	1.09
			1.00
		Vigorous activity	
		<630 kJ·wk^{-1}	1.30
		630 to <1680	1.16
		1680 to <3150	1.07
		3150 to <6300	1.07
		≥6300 kJ·wk^{-1}	1.00

[a] RR recalculated with the most active group as the reference.
[b] MET hours per week in quintiles.

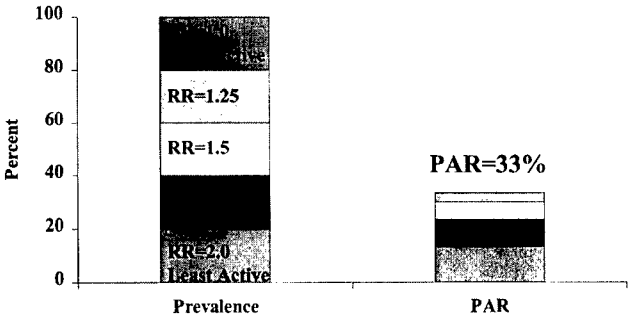


FIGURE 3—Prevalence distribution and PAR contribution: energy expenditure by quintiles, linear RR decline.

In spite of the difficulties of calculating and interpreting PAR estimates for general populations, there is sufficient information to make some informed estimates of the effect of the shape of the dose-response curve. Using theoretical estimates of RR and assuming a fixed prevalence (quintiles), PAR estimates that might be applicable to general populations with these characteristics can be calculated. In these examples, the reference group (RR = 1.0) is the most active 20% of the population and the highest risk group (RR = 2.0) is the least active 20%. The RR for the other quintiles varies depending on the shape of the dose-response relationship. In Figure 3, a linear relationship is assumed, and the RR for each quintile increases by 0.25 as activity decreases (1.0, 1.25, 1.50, 1.75, 2.0). The overall PAR is 33%, and each quintile's contribution to the overall PAR is shown (Fig. 3). About 70% of the overall PAR is attributable to the least active quintiles. In Figure 4, the same prevalence estimates are applied, but the RR increases in a nonlinear manner as activity decreases (1.0, 1.125, 1.25, 1.5, 2.0). In this example, the overall PAR is 27% and about 82% is attributable to the two least active quintiles. Understanding the shape of the dose-response relationship between physical activity and target health outcomes can provide improved estimates of the effect of changes in physical activity patterns on a population level.

In summary, PAR can be a useful tool to understand the public health burden of physical inactivity and to further quantify the implications of different doses of

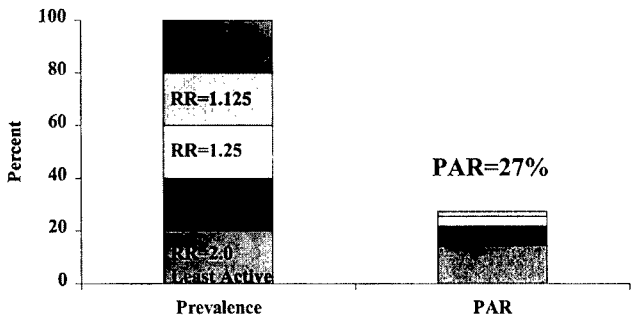


FIGURE 4—Prevalence distribution and PAR contribution: energy expenditure by quintiles, exponential RR decline.

physical activity. However, its usefulness would be improved if the following recommendations were implemented:

- Develop prevalence and relative risk estimates that can be applied to the entire population by using consistent definitions of physical activity intensity in both research and surveillance settings.
- Develop methods to model the benefits of the combined health effects of different doses or intensities of physical activity on health outcomes.

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Chair summary and contents

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The three articles in this session are all related, in one way or another, to issues of dose-response from the perspective of population health. The first article, by Williams (6), deals with the issue of whether the health benefits of an exercise intervention arise from the exercise itself or from body fat loss consequent to the exercise. The second article, by Wilmore (7), investigates the issues of age, sex, and health status variation in blood pressure and lipid responses to exercise, which relates to exercise prescription and whether one set of physical activity recommendations would be sufficient for the entire population. The final article, by Macera and Powell (4), highlights the issues and problems surrounding the use of population attributable risk (PAR) estimates in the study of physical activity and health.

The article by Williams (6) highlights the complexity of the relationships among physical activity, adiposity, and health outcomes. For example, cross-sectional population studies indicate that the relationship between physical activity and high-density lipoprotein cholesterol (HDL-C) are largely independent of body fatness; however, intervention studies suggest that the exercise-induced increases in HDL-C are associated with the decreases in body fatness that accompany the exercise. Regardless of the mechanisms behind the observed increases in HDL-C, it is important to remember that the alterations in HDL-C levels are the result of increases in physical activity (through exercise-induced fat loss or another pathway).

It is difficult to tease out the effects of exercise *per se* versus exercise-induced fat loss on the basis of mean responses to exercise. For example, if a significant mean increase in HDL-C resulted from an exercise intervention that elicited a significant mean increase in aerobic fitness but no significant mean decrease in body fat, the increased HDL-C may not be directly attributable to the increase in aerobic fitness. One would have to examine individual responses to the intervention, and correlations among the changes in fitness, fatness, and HDL-C may provide some insights. Future studies aimed at investigating the mechanisms behind dose-response issues should focus on individual responses to exercise rather than relying on mean changes.

As pointed out by Macera and Powell (4), it is important to remember that the PAR is a *theoretical* estimate of the burden of a particular risk factor on a given society. It cannot be assumed that it will be possible to have every physically inactive individual in a society become physically active. This approach was taken by Powell and Blair (5), who provided "realistic" estimates of the public health burden of sedentary living. Although it does have limitations, the PAR remains a powerful tool to evaluate the potential impact of public health policies and programs. For example, a public health objective in Canada is to reduce the prevalence of physical inactivity by 10% over the 5-yr period 1998–2003 (3). The prevalence of physical inactivity in Canada in 1997 was 62% (2); thus, a 10% reduction would result in a prevalence of 56%. Assuming a relative risk of 1.9 for coronary heart disease (CHD) (1), the PAR would drop from 35.8% to 33.5%. Thus, a 10% reduction in the level of physical inactivity could theoretically return a 6% decrease in CHD in Canada.

According to Wilmore (7), response to exercise training in blood lipids and blood pressure, although not affected by age, appear to be attenuated in female participants, and appear to be elevated in unhealthy people. Given that targeted reductions in the prevalence of inactivity may not be uniform across sex and health status, projected changes in disease burden, on the basis of simple calculations of PAR, may not be truly reflective of what is going on. Future studies should attempt to model PAR estimates using samples stratified by sex, and health status.

We must develop a worldwide perspective on dose-response issues surrounding physical activity and health. Methods of physical activity surveillance and definitions of physical activity not only vary from country to country, but also within countries, as pointed out by Macera and Powell (4). Prevalence estimates are generally presented using a variety of arbitrary cutoffs, which often change over time as physical activity recommendations change. It is also likely that the RR estimates for physical activity may vary from population to population, even for a standardized physical activity definition. Future research should be aimed at examining issues of dose-response in different populations and ethnic groups, an area that we know little about at the present time.

SUMMARY

1. Relationships among adiposity, physical activity, and health outcomes are complex. Adjustment for adiposity (usually BMI) in population studies rarely alters the relationship between physical activity and health

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outcomes, and in particular, HDL-C levels. However, changes in HDL-C with exercise training are associated with the changes in adiposity consequent to the training. A statistical adjustment model derived from exercise training studies has been proposed that may clarify the relationships among adiposity, physical activity, and health outcomes in cross-sectional studies.

2. Age has little if any effect on the response to exercise training for SBP, DBP, TG, and HDL-C; females appear to have an attenuated response compared with males for SBP, DBP, and HDL-C, with equivocal results for TG; and unhealthy subjects (hypertensive and post-MI) seem to have a more favorable response in DBP, SBP, TG, and HDL-C to exercise than healthy subjects.
3. Population attributable risk estimates would benefit from coupling RR estimates with population prevalences and better defined RR estimates for various doses of physical activity.

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