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RISK FACTORS FOR OSTEOPOROSIS ARE ASSOCIATED WITH
STRESS FRACTURE IN YOUNG WOMEN

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Running head: Stress fracture associations

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The views, opinions, and findings in this report are those of the authors and should not be construed as an official Department of the Army position, policy or decision.

KEY WORDS: sampling studies; stress fracture; menstrual status; amenorrhea; ethnic; smoking--complications; family characteristics; osteoporosis; age factors; body weight; exercise; parity; pregnancy; menarche; contraceptives, oral; premenopausal; military; soldiers

Abstract

Several factors which affect bone density and predict risk of osteoporosis have been reportedly associated with a higher incidence of stress fracture in young active women (e.g. amenorrhea, ethnic origin). This study surveyed the prevalence of ever having been diagnosed with a stress fracture in a large population of healthy premenopausal women and examined the association with risk factors for osteoporosis. A mail survey was delivered to 2312 active duty Army women (mean age: 26.1 $\pm$ 5.8(SD) yrs) and questionnaires were returned by 70.5% (1630) of this sample. Stress fracture had been previously diagnosed in 16.1% (263) of the respondents. Current smoking, previous history of amenorrhea (menses absent > 6 months), and known family history of osteoporosis were associated with history of stress fracture, while black ethnic origin appears to have been a protective factor. Age was inversely associated with stress fracture, probably reflecting selective processes specific to this population. This data suggests hypotheses for stress fracture (risk factors) which bear further testing. *These* *pathogenesis?*

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INTRODUCTION

Women in the United States now participate in exercise programs more than ever before. A subset of these women will develop stress fractures as a consequence of the increase in weight-bearing exercise (1,2). This is particularly a problem for women, ^{since they} who are at substantially higher risk for stress fracture than men. This difference has been noted in military basic training where 10-12% of women suffer stress fractures compared to an incidence of 1-3% of men participating in the same training (2-4). More recent attention has been devoted to stress fracture in amenorrheic athletes, where menstrual status appears to ^{play a role in determining} further differentiate which women ^{will be} are most susceptible to stress fracture (5).

Bone remodeling is part of a normal response to physical stressors and this is generally expected to result in a stronger bone (6,7); however, in some susceptible individuals, a debilitating fracture occurs in remodeled sites before the changes are complete (2,8). Presumably this risk is greater in individuals with lower bone densities and may be related to some of the same factors which predict risk of osteoporosis in women. These factors include asian or caucasian race (9,10), family history of osteoporosis (11), underweight (12,13), exercise (14) and factors related to a reduced estrogen level such as smoking (15), episodes of amenorrhea (16), and post-menopausal status (17).

Our survey was designed to address some of the shortcomings in the literature on stress fracture, specifically to determine the prevalence of women experiencing stress fractures and the associated factors which are present in these women. This was performed with an Army population which consisted of largely premenopausal, physically active women, lacking significant chronic illness.

METHODS

A questionnaire was developed which asked eighteen questions about the presence of factors associated with reduced bone density. The questions were brief and called for simple answers. An initial version of the questionnaire was administered to 50 soldiers who were then interviewed by a physical therapist (J.R.D.) about their responses; the final form was a refinement based on this test survey.

To establish an operational definition of stress fracture, the key question asked was "Has a doctor ever told you that you had a stress fracture?"; this was followed by "If YES, what part of your body?". Positive responses to this question followed by a plausible description of the site of injury were scored as women who have had a stress fracture. The stress fractures most likely to be correctly diagnosed at a general medical treatment facility would generally be categorized as symptomatic, either with debilitating pain or frank fractures (2).

We defined "amenorrhea" as a six month absence of menses, not associated with pregnancy. Family history of osteoporosis was indicated from "did your mother or your grandmother develop a hunched-over appearance or break ^{thru hips} her hip?", if this information was known. Weight trends were assessed by asking the women if they had ever exceeded Army weight standards (i.e. body mass index $> 23-24 \text{ kg/m}^2$) and if they had ever been told that they were underweight.

The questionnaire was mailed to the duty addresses of 2462 active duty female soldiers identified by a computerized personnel database system at Fort Lewis, Washington in July 1987. The questionnaire was accompanied by a short letter signed by a female Army physician (J.A.N.) soliciting participation in the study. Soldiers were also provided preaddressed

stamped envelopes to return the questionnaires and they were asked to return separately an identifying postcard indicating whether or not they planned to return a survey form. Completed surveys were returned by 1295 soldiers; 1288 postcards were also returned with 8 which indicated that the subjects would not participate. Four weeks after the first mailout, a second copy of the survey was sent to 1092 soldiers who were presumed to have been reached by the first survey but had not returned a postcard. They were encouraged to return a survey if they had not already done so. A total of 1630 out of 2312 (70.5%) deliverable questionnaires were returned within 10 weeks of the first mailout and these were used in the analysis.

Factors associated with reported stress fractures were contrasted using a contingency table format with a chi-squared test. Logistic regression was performed to determine the strength of the association between significant factors and stress fractures. The Mantel-Haenszel chi-squared test was used to examine the effect of age and ethnic origin on the other factors (BMDP87, Los Angeles, CA).

RESULTS

The mean age in the survey sample was 26.1 ± 5.8 (SD) yrs (median age: 24 yrs; range: 18-52). The ethnic breakdown of respondents was 57.1% nonhispanic caucasian, 32.8% black, 5.0% hispanic, 2.2% asian, and 2.9% other or unspecified. Other known characteristics of the survey sample are presented in Table 1.

In this sample, 16.1% of women had experienced a stress fracture. The most prevalent location for a stress fracture was the lower leg (53.2% of stress fractures reported) (Table 2).

Table 1 compares the percentages of women with a history of stress fracture in subpopulations of women with or without osteoporosis risk factors (chi-squared test). Analysis by stepwise logistic regression yielded 5 factors independently associated with stress fracture: history of amenorrhea, current cigarette smoking, non-black ethnic origin, known family history of osteoporosis, and young age. Age, was included in the logistic analysis as a continuous variable and the skewed distribution was normalized with a log transformation. All of these terms and the likelihood ratio for the logistic model were significant at a probability level of 0.005 or less.

Based on the logistic analysis, the probability of ever having had a stress fracture ranged from 31.6% in a non-black, smoker, with episodes of amenorrhea and a family history of osteoporosis down to 8.0% for a black, non-smoker, with normal menstrual history and a negative family history, or a four-fold difference. Relative risks (and 95% CI) determined from the logistic analysis for amenorrhea, smoking, non-black ethnic origin, and family history were 1.36 (1.25-1.48), 1.32 (1.23-1.41), 1.28 (1.17-1.39), and 1.25 (1.16-1.35), respectively.

Age was also a significant factor in this sample, but in an inverse relationship with stress fracture history. Thus, from the logistic regression, older women with none of the four other risk factors would have a predicted prevalence as low as 1.5%; the actual prevalence in our sample for all women over age 40 (n=42) was 1.4%, compared to the highest overall prevalences of 19.6% for women aged 22-23 (Figure 1). This is a likely consequence of selective processes in this specific military population, as will be discussed. Dividing the sample roughly in half (age 25), age was a significant covariate for the prevalence of stress fracture by each of the other factors: ethnic origin, smoking, family history, and amenorrhea (Mantel-Haenszel, $p < 0.001$). Crude odds ratios from the individual factor chi-squared tables were similar ^{to} but slightly higher ^{than} ~~compared to~~ those derived from the logistic analysis (Table 3). Amenorrhea had a significant effect on stress fracture prevalence only in the younger women (29.9 vs 16.0%, $p < 0.001$) compared to women > 25 years old (18.2 vs 12.7%, $p = 0.12$). Age was also a significant cofactor for underweight, with only the younger women demonstrating a significant relationship between stress fracture and being underweight ($p < 0.05$; Mantel-Haenszel test, $p < 0.05$). Other expected age related factors such as having had a baby increased with age (Figure 1) but had no detectable association with prevalence of stress fracture history.

Black women were significantly more likely to have had children (51.5 vs 36.8%; $p < 0.001$), were more likely to use oral contraceptives (40.9 vs 31.6%; $p < 0.001$), and were less likely to be current smokers (32.1 vs 37.8%; $p < 0.001$), all factors which have been reported to be protective against stress fracture and osteoporosis. These latter two differences are accounted for by a high proportion of younger black women, since the prevalences of current smoking and oral contraceptive use were also higher

in younger women (< 25 years). Only 12.0% of black women reported a family history of osteoporosis, while 38.2% of non-black women reported positive family histories; nevertheless, a positive family history of osteoporosis was associated with a 10% higher prevalence of stress fractures, with no difference between blacks and non-blacks ($p=0.62$), while ethnic differences in stress fracture were apparent only when family history of osteoporosis was negative ($p<0.01$; Mantel-Haenszel chi-square test, $p<0.01$).

A positive history of amenorrhea had a significant effect on the relation between smoking and stress fracture, with more stress fractures in smoking (vs nonsmoking) women without history of amenorrhea (20.3 vs 11.6%, $p < 0.001$) but with no differences in women with history of amenorrhea (28.6 vs 21.8%, $p = 0.23$) (Mantel-Haenszel test, $p < 0.001$). Smoking had a comparable effect on the relation between amenorrhea and stress fracture, with a significant relation in nonsmokers ($p<0.001$) but not in smokers ($p=0.08$) (Mantel-Haenszel test, $p < 0.001$). More women had experienced episodes of amenorrhea in the subpopulations of women who had (ever) been told that they were underweight (23.7 vs 13.2%) and who were runners (>10 miles/week) (20.3 vs 13.4%) ($p < 0.05$).

DISCUSSION

The prevalence of clinician diagnosed stress fracture reported by the women in this survey (16.1%) is consistent with other reports. Eleven percent of the women surveyed reported that they had bone pain which was sufficiently debilitating that they had to stop running during basic training. Thus, it is probable that many of the reported stress fractures occurred in basic training, at a rate which is comparable to the 10.5% observed in a group of 114 female Marine recruits during basic training (18), 10.0% observed in the first 8 week training period at the US Military Academy (4), and 11.3% observed in 186 Army recruits in basic training (2). Assuming in the worst case that all of our nonrespondents were disinterested women with no history of stress fracture, we would still have a stress fracture prevalence of greater than 10%.

Most previous studies of stress fracture have been conducted with elite athletes and little is known about risks to the general population, which may be better represented by our sample of women in the Army. This sample is skewed towards younger women and it excludes individuals with conditions which significantly affect physical performance since this is a condition of continued Army employment; therefore, this study yields information about healthy young women. Generalization about older active women must be made with caution because of the selective processes which determine their presence in this study sample. Also, the intensity of physical training which Army women are subjected to in basic training (where stress fractures tend to emerge) increased markedly in about 1978, representing another age related confounder in this cross-sectional data which may explain the inverse age relationship to stress fracture prevalence.

The association of smoking with stress fracture is one of the most interesting findings to emerge from this study. Cigarette smoking has been associated with osteoporosis or reduced bone mineral content (15,19) while other studies have failed to demonstrate a connection (20). To our knowledge, our results provide the first demonstration of such a relationship to stress fractures in a population which is almost entirely premenopausal. Smoking reduces serum estrogen levels in a dose-related relationship, possibly through a nicotine induced increase in hepatic metabolism (21,22). This reduction in estrogen levels has been linked with a trend to reduced bone mineral density in smokers (21). In this survey, current smokers had a higher prevalence of stress fracture than women who were former smokers or who had never smoked. These findings are particularly important since smoking is a modifiable factor. We did not find any additional differences in stress fracture between duration of smoking (analyzed as a continuous variable; data not shown) or smoking more than one pack per day in the current smokers.

Amenorrhea is another factor identified in this study which may be modifiable, through physician intervention. Like smoking, the effect on bone is presumably produced by episodes of hypoestrogenism (16,23,24). Indeed, women with a history of amenorrhea did not have a significantly higher prevalence of stress fracture if they also smoked, nor was there a significant association between amenorrhea and stress fracture in women who smoke, suggesting a single mechanism by which these two factors may produce a marked susceptibility to stress fracture. Our data confirms previous findings in collegiate women athletes, where stress fractures were observed in 24% of women with irregular or absent menses but in only 9% of the women with normal menses (5). The connection between amenorrhea and reduced bone density is implied by the increase in bone density which occurs in

amenorrheic athletes with a resumption of their menses (25). This data strongly suggests that in women engaged in vigorous weight-bearing activities such as running or marching, amenorrhea is a symptom which may signal higher risk of bone injuries. Measures should be taken to return such individuals to normal menstrual patterns. Other protective measures might include reduced training volume or the prescription of estrogens (with opposing progestagens) by a physician if a significant reduction in bone density is established.

Lloyd et al. (5) found that risk of stress fracture was lower in those who used oral contraceptives. We did not find any significant relation to the use of oral contraceptives but this may be related to the difference in prevalence of amenorrhea in our study population. The prevalence of amenorrhea may be high in some athletes and, in these women, the low dose estrogen of many contraceptive preparations may offer some protection against bone loss. In contrast to athlete samples, only 14.9% of our population reported amenorrhea "ever" and only 1.3% of the nonpregnant women in our sample were currently amenorrheic (>6 months since last menses at the time of survey). This latter rate is similar to the point prevalence rate of 1.8% reported in a Swedish survey (26).

In our study, women running over 10 miles/week or having been told they were underweight were also more likely to have a history of amenorrhea, but these factors appear to be only loosely associated. Exercise serves as the stimulus for bone remodeling but whether this will result in an increase in bone density or in a stress fracture appears to be dependent on other factors such as previous ^{history?} of amenorrhea. This is suggested by our data, and by the results of studies of women athletes where the rates of stress fracture in eumenorrheic exercising women were

unremarkable (5). Intense exercise may be involved in amenorrhea, as evidenced by the return of menses in some amenorrheic women who reduce their exercise (27), but amenorrhea is not a necessary consequence of intense exercise (28). Similarly, low weight (or low body fat) does not necessarily produce amenorrhea (29). These three factors may be non-causally associated as common aspects of a behavioral and/or hypothalamic disorder (30). Underweight was associated with an increased likelihood of stress fracture in the younger women (≤ 25 years old). Although body weight is a factor in bone mass (31,32), underweight did not emerge as an independent factor associated with stress fracture in this study.

We did not ask about calcium intake and other dietary habits because of the difficulties in assessing these in a questionnaire. Nevertheless, dietary calcium may not play a major role in preventing bone loss except in infrequent serious deficiency conditions (33), although alcohol consumption is linked to reduced bone density (20) and, very recently, the surveyable factor of carbonated beverage consumption has also been related to an increased fracture rate (34).

Positive family history is recognized as a risk factor in osteoporosis (11) and a reduced bone mass has been demonstrated in relatives of osteoporotic patients (35). Family history was a factor associated with an increased prevalence of stress fracture in both black and non-black women in our study. Ethnic origin was a second unrelated hereditary factor associated with stress fracture. The reduced risk of osteoporosis in black women is associated with a greater bone density, perhaps as a result of reduced osteoclast activity (36); whether or not this reduced excavation of bone persists during an exercise induced remodeling remains to be demonstrated but the higher starting bone mineral density in black women is of itself likely to be protective of stress fracture, an association

confirmed in this study. Brudvig et al. (37) found that the one year incidence of stress fracture was 1.4 in black women compared to 11.8 in white women in a young population of basic recruits reporting to a physical therapy clinic; while the incidence was lower in males there was still a lower incidence in black males than white males, and our data confirms this protective effect of black ethnicity on stress fracture.

This study suggests hypotheses for further investigation, specifically the possibility that smoking, amenorrhea, and family history of osteoporosis are risk factors for stress fracture in young women, while black ethnic origin may be a protective factor.

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Table 1. Prevalence of stress fracture in association with surveyed factors. Ranked in order of factor prevalence in the sample.

Factor	Percent of total with factor	Percent with history of stress fracture		
		factor present	factor absent	
Ethnic origin (caucasian or asian)	67.3	18.5	11.3	***
Nulliparity	58.4	16.1	16.2	
- gynecological age ≤ 20 (1)	(16.6)	19.3	14.5	
- more than 2 births (1)	(12.7)	15.4	17.0	
Age (≤ 25 years)	44.8	18.2	13.6	**
Cigarette smoking (ever)	55.1	19.4	12.0	***
Cigarette smoking (current)	34.6	21.9	13.1	***
- have smoked for >10 yrs (2)	(30.4)	24.8	20.4	
- more than one pack/day (2)	(19.2)	24.6	20.7	
Current oral contraceptive pill use	34.6	17.6	15.1	
Ever on the Army Weight Control Program (BMI > 23 -24 kg/m ²)	31.0	16.9	15.7	
Family history of osteoporosis	29.8	21.8	13.5	***
Running exercise (>10 mi/wk)	21.0	19.0	15.4	
Ever told that they were underweight	16.9	20.5	15.4	*
History of amenorrhea (episodes of ≥ 6 months)	14.9	22.7	13.4	***
Late menarche (>16 yrs old)	3.6	19.0	16.1	

chi-squared test; significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
subsamples: (1) parous women (n=698); (2) current smokers (n=581).

Table 2. Location of medically diagnosed stress fractures.

Location	Number	Proportion of all stress fractures (266)	Prevalence in overall sample (1630)
Pelvis	15	5.6 %	< 1.0 %
Hip/upper leg	23	8.7	1.4
Lower leg	140	53.2	8.6
Foot	74	28.1	4.5
other	11	4.2	< 1.0
	263	* 99.9 %	16.1 %

*total is less than 100% due to rounding

Table 3. Odds ratios of factors associated with stress fracture, stratified by age.

factor	age group	odds ratio	prob	pooled odds ratio (95% confid interval)
amenorrhea history	≤ 25	2.24	.0002	1.93 (1.37-2.72)
	> 25	1.53	.12	
current smoker	≤ 25	1.96	.0001	1.91 (1.45-2.51)
	> 25	1.84	.005	
ethnic origin (caucasian/asian)	≤ 25	1.78	.003	1.82 (1.33-2.50)
	> 25	1.94	.02	
family history	≤ 25	1.66	.01	1.88 (1.38-2.55)
	> 25	2.22	.0007	

LEGENDS

Figure 1. Respondent age distribution (bars) and current smoking and prevalence of stress fracture by age. The line graph data is expressed as a three point running mean.

Figure 2. Age-related prevalence of parity, oral contraceptive pill use, and menstrual irregularity in active duty Army women. Data is expressed as a three point running mean.

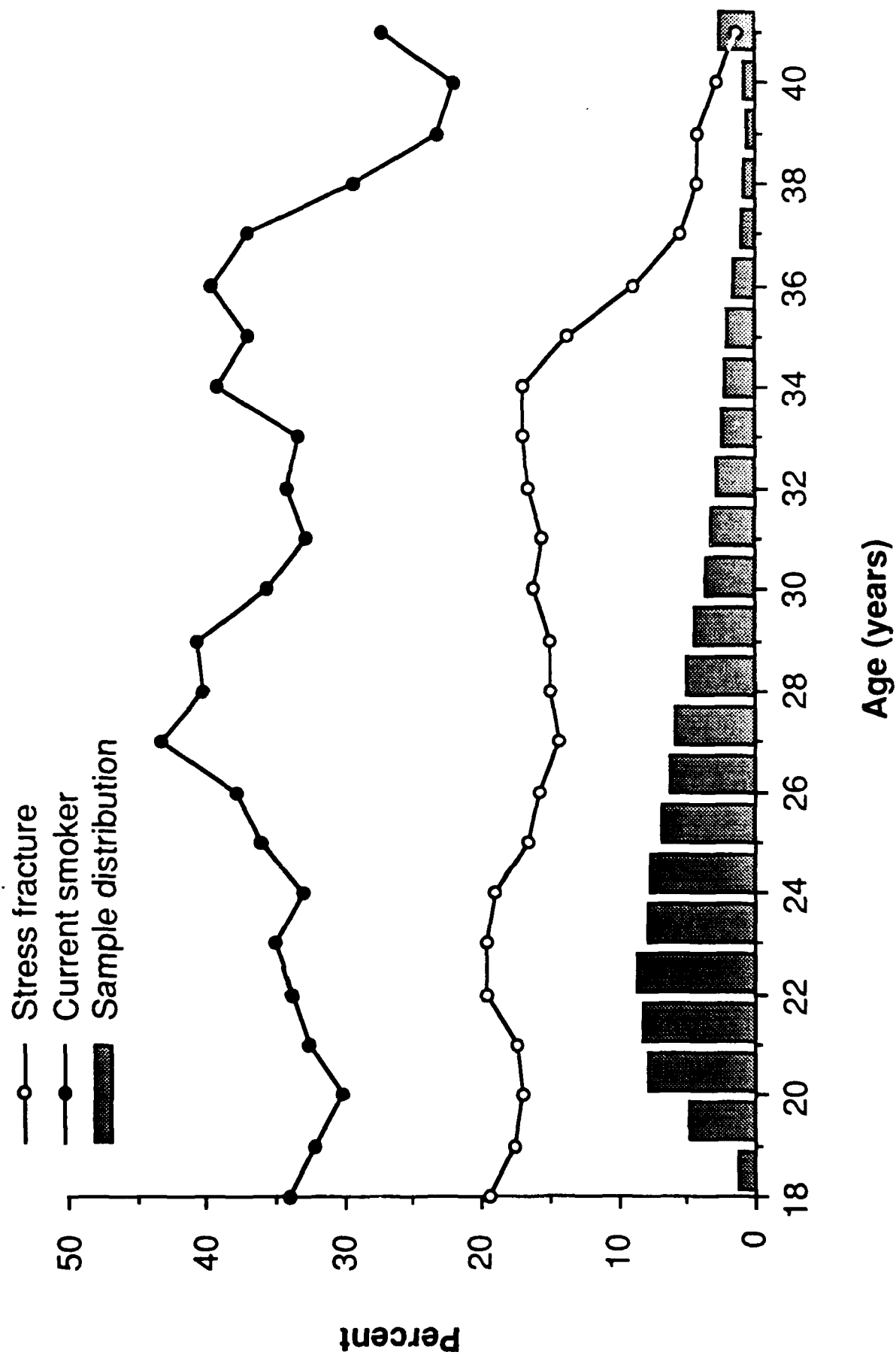


Figure 1

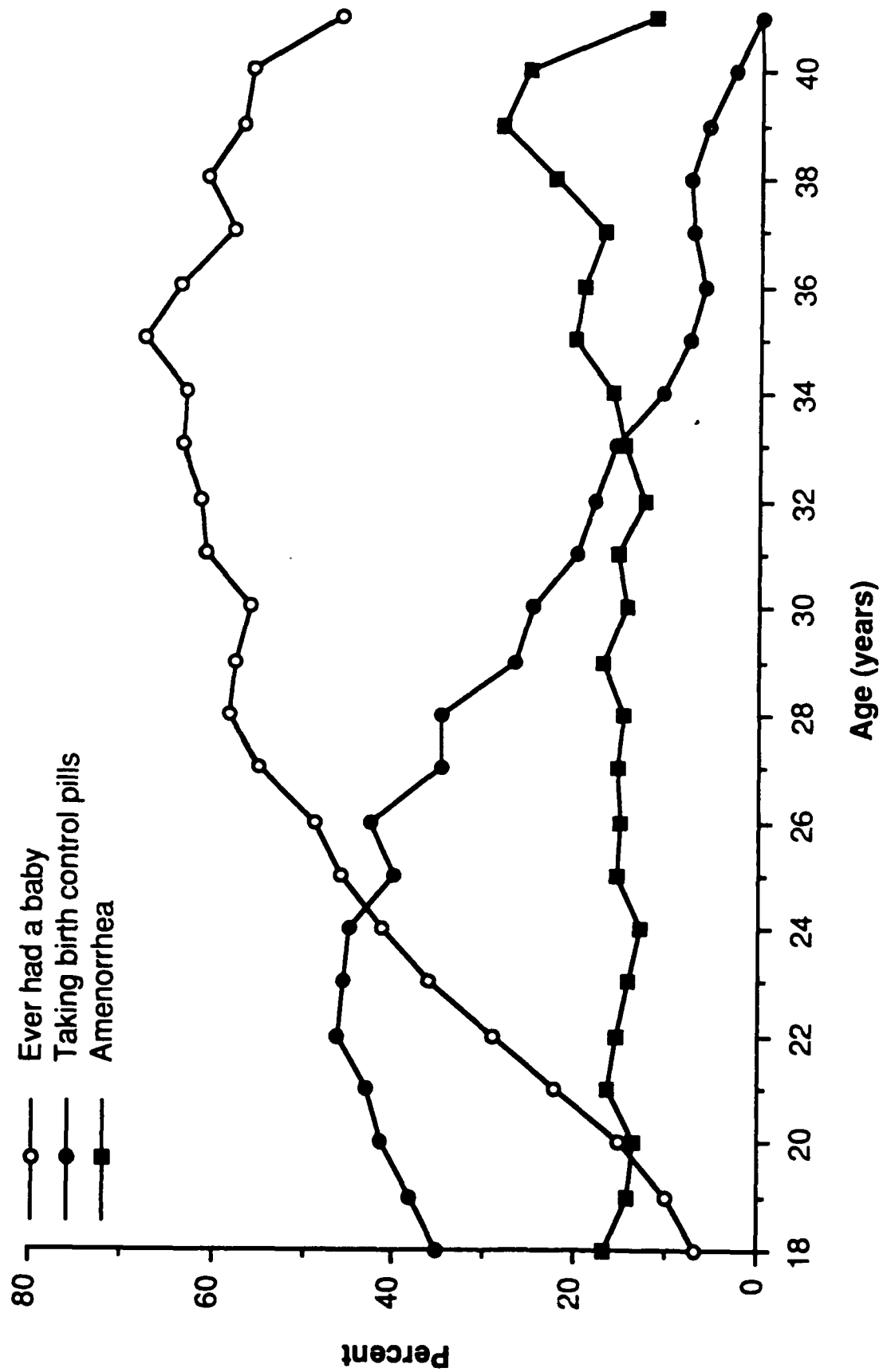


Figure 2