

The Millennium Cohort Study

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For the Millennium Cohort Study Team

ABSTRACT

Introduction and Relevance

Concern has been raised in the decade following the Persian Gulf War of 1990-91 that military service, and operational deployments in particular, may lead to long-term health problems. Chronic, multi-symptom illnesses have been especially challenging to assess in post-deployment troops. Retrospective epidemiologic analyses have been both difficult and costly for the US Department of Defense.

Rationale

US policymakers, academicians, and veterans groups called for a prospective cohort study to better assess the relationship between chronic health problems and military service.

Methods

Beginning in 2001, the Millennium Cohort began enrollment of a stratified random sample of more than 140,000 service members, with the intention of following their health for up to 20 years. Cohort members will provide self-reported data on medical symptoms, functional status, and health-related behavior every 3 years. New and existing sources of objective data on health and health-related exposures, both during and after service, will be leveraged and linked to the cohort at regular intervals over the next 20 years.

Results

Nearly 80,000 service members enrolled in the Millennium Cohort in the first phase of the study. Participants are demographically well representative of the target population. Enrollment surveys demonstrate greater than 95% completion rates. Initial data capture from all sources, including internet-based surveys, is rapidly progressing.

Conclusions

The Millennium Cohort Study has been successfully launched. This 20-year project is expected to better define the long-term health of US military service members. The study's ability to prospectively evaluate both objective and subjective health status, in relation to deployments and other occupational exposures, will make results of high interest to both military and civilian public health professionals.

Paper presented at the RTO HFM Symposium on "NATO Medical Surveillance and Response, Research and Technology Opportunities and Options", held in Budapest, Hungary, 19-21 April 2004, and published in RTO-MP-HFM-108.

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE 00 JUN 2004		2. REPORT TYPE N/A		3. DATES COVERED -	
4. TITLE AND SUBTITLE The Millennium Cohort Study				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Director, DoD Center for Deployment Health Research Naval Health Research Center, Code 25 Box 85122 San Diego, CA 92186 USA				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited					
13. SUPPLEMENTARY NOTES See also ADM001747, RTO-MP-HFM-108, NATO Medical Surveillance and Response, Research and Technology Opportunities and Options (La surveillance médicale et les réponses au sein de IOTAN: les possibilités et les options pour la recherche et la technologie)., The original document contains color images.					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 6	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

1.0 BACKGROUND

In 1990 and 1991, the United States (US) deployed more than 700,000 military service members to the Persian Gulf region as part of Operation Desert Shield and Operation Desert Storm. The troops' engagement was brief and very successful by all military standards. In the wake of these deployments, however, some service members raised concern about medical problems that they attributed to their service. Their medical concerns included a wide range of problems, including injuries, infectious diseases, mental health challenges, and ill-defined, chronic, multi-symptom illnesses. Over the next ten years, countless hours and more than \$1 billion (US) were expended exploring the issue of "Gulf War-related illnesses." [1,2]

Past studies of post-deployment health problems were all retrospective in design. Epidemiologically, such designs are challenged by confounding, selection of appropriate control groups, response biases, and recall biases. In responding to the concerns of deployers from the Gulf War, clinicians, policymakers, and researchers were frustrated by such study designs. In 1999, the US Institute of Medicine issued a report calling for a large prospective study to better define the long-term health risks of military occupations and deployments. [1] The US Department of Defense also formally recognized the need to coordinate such a prospective evaluation of its service members. [2] In response, the Millennium Cohort Study was developed. [3]

2.0 METHODS

The Millennium Cohort Study investigators include epidemiologists from all branches of the US military services as well as the US Department of Veterans Affairs. The original protocol was developed with considerable input from leading cohort study researchers. A select Scientific Steering and Advisory Committee (SSAC) was commissioned, composed of premier academic epidemiologists to closely guide the study over time. The Millennium Cohort SSAC also includes representatives from leading US veterans' service organizations, such as the American Legion, in order to ensure that veterans' concerns are represented in scientific discussions.

The primary objective of the Millennium Cohort Study is to determine if risk factors related to military service, such as occupations, deployments, and other exposures, are associated with the development of chronic disease. Outcomes include objective medical diagnoses, such as those made during a hospitalization, as well as subjective symptoms and functional status. To assess such outcomes, investigators rely on serial survey evaluations of cohort members, and linking to many objective health-related databases. Objective data sources include automated healthcare encounter data, both inpatient and outpatient, from both military and civilian facilities, pharmacy data, immunization data, occupational data, exposure data, disability data, and mortality data. It should be noted that not all such databases were available or complete in the era immediately after the 1990-91 Gulf War.

Power to define a wide range of illnesses requires a large sample size. Approximately 140,000 service members will ultimately be enrolled in the Millennium Cohort. Nearly 80,000 were enrolled in the first phase in 2001. An additional 40,000 will be enrolled in 2004, and 20,000 more will be enrolled in 2007. All will be followed through 2021. In total, the study will include more than 2,500,000 person-years of follow-up. Original participants were invited from a random sample of more than 250,000 men and women in the US military in 2001. The sample was stratified to include adequate representation of those with a past history of deployment, women, and those in the US National Guard and Reserve forces. Invited personnel in 2004 and 2007 will be drawn from random samples of service members with fewer than two years of service at the time

of enrollment. This will ensure that the Millennium Cohort will adequately represent current forces and recent deployments.

The enrollment survey was developed with expert consultation, using standardized instruments whenever possible. It contains a consent form and a comprehensive battery of questions evaluating past medical problems, mental health issues, symptoms, functional status, health-related behaviours (such as tobacco and alcohol use), and self-reported occupational and environmental exposures. The survey may be completed on paper and takes approximately 30 minutes. Importantly, participants may also enroll and complete their surveys over a secure internet site, www.millenniumcohort.org. On-line completion takes less than 30 minutes and receipt of data by the investigative team is almost immediate. Participants enter unique identifying numbers to access the survey on-line, and their private information is managed with the highest levels of security. Enrolled participants will be asked to complete a follow-up survey every 3 years for the duration of the project.

At the inception of the Millennium Cohort, it was recognized that maintaining the engagement of participants over the life of the study would be challenging. Most US military members spend only 3-5 years in service, so follow-up includes much post-service civilian time. Potential participants are invited to join the cohort using modified Dillman methods that include alternating postcards and survey mailings. Email invitations, carefully phrased to not appear to be “spam” email, are also used. Marketing consultation is sought to develop efficient and effective text for such invitations. Citing endorsement of the study by the US Deputy Secretary of Defense has been helpful in reassuring some participants of the legitimacy of the project. To maintain engagement and foster a sense of cohort identity, enrolled participants receive “thank you” postcards every six months, on US Memorial Day (May) and Veterans Day (November) holidays.

It is recognized that collection of participants’ data over the internet site has many advantages. This mode of data collection saves time and tremendous resources in postal contact. It also results in cleaner data that require no scanning or verification prior to analyses, saving many more study resources. Given these advantages, participants are encouraged to provide data on-line through incentives (cost-saving initiatives), in the form of a hat, T-shirt, or phone card, in appreciation for their use of the secure internet site. The Millennium Cohort tokens they receive serve the secondary purpose of enhancing cohort identity and motivation to continue long-term participation. In addition, use of the internet site allows sharing of general study information and updating of contact information. This is considered important for this mobile population of young adults.

3.0 RESULTS

A pilot test of Millennium Cohort enrollment, focused at a 1% random sample of potential participants, was completed in May 2001. Invitations for enrollment in the full cohort were initiated in July 2001. The first enrollment year was marked by challenges related to the terrorist attacks on the US on September 11, 2001. These events resulted in rapid mobilization and deployment of many military members, making them more difficult to contact. In addition, anthrax contamination was discovered in the US postal system in October 2001, resulting in many months of mail delays and non-delivery throughout the country. Despite these challenges, repeated attempts to contact potential participants resulted in more than 77,000 members consenting and enrolling in the Millennium Cohort. Greater than 50% of participants provided their information over the secure internet site, www.millenniumcohort.org.

To date, the study team has performed extensive analyses of data quality. Question-by-question completion rates for the survey, on both the internet and paper versions, have been evaluated. Despite the length of the

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survey and personal nature of the health questions, no survey question had a completion rate lower than 80%. Most questions were completed by more than 95% of participants. Question-by-question completion rates for surveys received over the internet were consistently higher than paper survey completion rates.

The study team has been concerned about response bias, that is, how well do Millennium Cohort participants represent the entire US military. Multivariable logistic regression analyses have compared responders to non-responders, including all available demographic variables in statistical modeling. Investigators have found that responders are statistically slightly more likely to be older, more highly educated, of white race/ethnicity, female, married, officers, in the Reserve of National Guard forces, and to work in the fields of communications, intelligence, health care, technical support, or functional support. It is notable that the odds ratios associated with these demographic differences ranged from 1.1 to 1.7. When health outcomes are analyzed, investigators will be able to control for these small demographic differences in multivariable modeling.

The study team has also been concerned that survey responders may have different baseline health characteristics than non-responders. To date, an analysis of healthcare utilization in the 12 months prior to 2001, among both respondents and non-respondents, has been conducted using data from the pilot study. Survey responders averaged 3.3 days of healthcare use and non-responders averaged 2.9 days of healthcare use. The difference was not statistically significant in multivariable modeling. Although this implies that there is little or no difference in baseline health between Millennium Cohort participants and others in the US military, continued analyses will explore this important issue among the full cohort.

Finally, the study team has wanted to ensure that differential access to the internet did not create a response bias. Multivariable logistic regression modeling, comparing internet respondents to paper respondents revealed that internet respondents were slightly more likely to be on active duty (as opposed to Reserve or National Guard forces), male, non-black race/ethnicity, married, between 25 and 35 years old, high school graduates, and working in the fields of electronics, communications, intelligence, functional support, or other technical specialty. Since the odds ratios associated with these differences were small (1.1 to 1.5) the differences do not appear large enough to bias study results.

Investigators will continue to examine these issues, and other important questions related to data quality and representativeness, in preparation for long-term evaluation of health outcomes in the cohort.

4.0 CONCLUSIONS

The Millennium Cohort study has been successfully launched. This ambitious 20-year project, following nearly 140,000 participants, is expected to better define the long-term health effects of military service. The study's ability to prospectively evaluate both objective and subjective health status, in relation to deployments and other occupational exposures, will make results of high interest to both military and civilian public health professionals.

Collaborative studies have already been proposed by both federal and academic institutions, and guidelines for evaluating collaborative protocols have been developed. The first health outcomes-based studies will include:

- Evaluation of mental health, prior and subsequent to the terrorist attacks of September 11, 2001,
- Evaluation of anti-malarial medication use and potential relationship to long-term health challenges,
- Evaluations of potential health changes associated with deployments to US Operation Enduring Freedom and Operation Iraqi Freedom.

The Millennium Cohort is a large, resource-intensive effort. External oversight is needed and welcomed by the investigative team. The primary protocols, and all sub-study protocols, are designed with external consultation. Multiple human use (ethical) review boards evaluate the project at least annually. The funding organization coordinates external scientific review by the American Institute of Biological Sciences approximately biannually. The US Armed Forces Epidemiological Board, which includes premier scientists from academia, acts as a public health advisory body to the study team. In addition, the study-specific Scientific Steering and Advisory Committee, comprised of leading US epidemiologists and veterans service organization representatives, provides invaluable insight to investigators.

This project will answer health questions about military occupations, and it is likely to serve as the foundation for many future epidemiologic studies. Its prospective design, size, and ability to capture a full range of health-related exposures and outcomes will make results valuable to both military and civilian communities. The results of the Millennium Cohort study are likely to resonate in public health for years to come.

ACKNOWLEDGMENTS

Co-investigators on the Millennium Cohort Study include: Paul Amoroso, MD, MPH, Edward Boyko, MD, MPH, Gary Gackstetter, DVM, PhD, Gregory Gray, MD, MPH, Tomoko Hooper, MD, MPH, and James Riddle, DVM, PhD. Research assistants on the study team in San Diego, California include: Gia Gumbs, MPH (coordinator), Suzanne Clark, Thomas Corbeil, Lesley Henry, Susan Hume, Sheila Jackson, Nick Martin, Robert Reed, MS, Besa Smith, MPH, Tyler Smith, MA, Steven Speigle, Timothy Wells, DVM, PhD, James Whitmer, and Sylvia Young, MD, MPH.

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- [2] US Secretary of Defense. Report to the Committee on National Security, US House of Representatives, and the Armed Services Committee, US Senate, on the Effectiveness of Medical Research Initiatives Regarding Gulf War Illnesses. Department of Defense, Washington, DC, 1998.
- [3] Gray GC, Chesbrough KB, Ryan MAK, Amoroso P, Boyko EJ, Gackstetter GD, Hooper TI, Riddle JR. The Millennium Cohort Study: a 21-year prospective cohort study of 140,000 military personnel. *Mil Med* 2002;167(6):483-8.

SYMPOSIA DISCUSSION - PAPER 31

Authors Name: Cdr Ryan (Speaker Cdr Young) (US)

Discussor's Name: Surg.Capt Hoejenbos (NL)

Question:

- 1) Is there an interaction between questionnaires used in study and the normal post-deployment questionnaire?
- 2) Is pre-deployment information used?

Author's Reply

- 1) The normal post-deployment health assessment questionnaire is independent from the Millennium Cohort Study questionnaire. Anyone who deploys is required to complete the post deployment health assessment questionnaire. Only a randomized sample is invited to complete the Millennium Cohort Study survey.
- 2) There is hope to link in the future with pre-deployment information from the recruit assessment program surveys which do collect baseline health information in military personnel upon entry into the service and this data can be used to augment pre-deployment information.

Authors Name: Cdr Ryan (Speaker Cdr Young) (US)

Discussor's Name: Dr Reifman (US)

Question:

What is the nature of the questions in the study (e.g. subjective, qualitative, etc).

Author's Reply:

The questions come from validated survey instruments such as the Patient Health Questionnaire (PHQ), SF-36 Medical Outcomes Short Form, and Patient Checklist (PCL) and are self-reported and subjective. Analyses linking with hard objective data such as information from the standard inpatient data record on hospitalizations and the standard ambulatory data record on out-patient visits are planned.

Authors Name: Cdr Ryan (Speaker Cdr Young) (US)

Discussor's Name: Dr Foster (US)

Comment on the Ryan/Young talk:

Millennium Cohort (MC) was designed as a formal, "Framingham" type, long term epidemiological study with funding from both the DoD research account and the DoD health care system. The questionnaire data collection is initial with periodic updates driven by date not by military status. The self-reported data from questionnaires are supplemented by data from visits to health care providers. This dual data gathering challenge will be ongoing for the next 20 years. Epidemiology research projects seeking to use MC data sets will be independently proposed, peer reviewed and funded. The "collaboration guidelines" provide guidance on how researchers can gain access to MC data for research.