

The US Department of Defense Millennium Cohort Study: Career Span and Beyond Longitudinal Follow-Up

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Objective: To describe current and future career-span health research in the US Department of Defense Millennium Cohort Study. **Methods:** Collaborating with all military service branches and the Department of Veterans Affairs, the Millennium Cohort Study launched in 2001, before September 11 and the start of deployments in Afghanistan and Iraq, to conduct coordinated strategic research to determine any effects of military occupational and deployment-related exposures, on long-term health. **Results:** More than 150,000 consenting members represent demographic, occupational, military, and health characteristics of the US military. More than 70% of the first two panels have submitted follow-up questionnaires and >50% have deployed since 2001. **Conclusions:** Prospective cohort data have identified subgroups of military populations at higher risk or more resilient to decrements in mental and physical health. Continued career span and beyond follow-up will answer long-term health questions related to military service. (J Occup Environ Med. 2009;51:1193–1201)

Cross-sectional and retrospective studies of exposures and health outcomes are capable of establishing associations but lack a more robust ability to distinguish exposure contribution in disease pathways. Causative roles of exposure to disease are better described through prospective analyses with appropriate comparison populations where subjects are disease free at baseline and followed over time to document exposure and disease through temporal sequence. Well-designed prospective cohort studies may have inferential leverage over cross-sectional and retrospective studies through the minimization of recall and selection biases that are often influenced by exposure and/or disease in retrospective or cross-sectional assessment of study populations. Well-known prospective cohort studies, such as the Framingham Heart Study, the British Physicians Study, and others, have made significant contributions toward improving public health.^{1–3}

Occupational cohort studies are often defined by a group of workers in a given occupation classified by certain exposures encountered on the job. Occupational cohort studies have been instrumental in identifying increased risk of cancer in workers exposed to gas,⁴ dyestuff,⁵ and asbestos⁶ and increased risk of mortality or morbidity from other occupational exposures.^{7–11} Prospective or historical prospective military cohort studies have also been conducted with some success in the past but have largely focused on single exposures.

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These studies have been designed post exposure, combat deployment, or conflict and have often lacked representativeness.⁶⁻⁹

The Millennium Cohort Study was envisioned to mitigate these limitations and construct a longitudinal heterogeneous cohort for comparisons of disease experience across subgroups defined by military service-related exposures.^{10,11} This large population-based cohort designed in the late 1990s was initiated in the aftermath of the 1991 Gulf War after the Department of Defense (DoD), Congress, and the Institute of Medicine recommended coordinated strategic research to determine how military service, including deployment-related exposures, affect long-term health.^{12,13} In collaboration with all military service branches and the Department of Veterans Affairs (VA), the Millennium Cohort Study was launched in 2001, before September 11 and the start of the wars in Afghanistan and Iraq.^{10,11} The Cohort includes military service members from all components (active duty, Reservists, National Guard members) and all services (Army, Air Force, Navy, Marine Corps, and Coast Guard). The objective of this report is to describe this DoD study, which follows service members for the span of their careers and beyond, and discuss strategic research goals that will answer health questions pertaining to military service for years to come.

Materials and Methods

Design and Objectives

The Millennium Cohort Study was designed in the wake of the 1991 Gulf War to complement many of the large electronic data that were beginning to become available to researchers. This Cohort was constructed to prospectively assess long-term health in all components and service branches of the US military and to follow them even after separation from military service with seven designed 3-year questionnaire

interval assessment periods. The original objectives of the Millennium Cohort Study included building a cohort of ~150,000 and assessing chronic diagnosed and subjective health problems, including hypertension, diabetes, heart disease, and chronic multisymptom illnesses among military members, in relationship to exposures of military concern. The average age of the cohort at baseline was 28.9 years. The newer military accessions that were invited in 2004 and 2007 were randomly selected (oversampling for women and Marine Corps members) and designed to complement the population-based random sample. More than 150,000 service members have voluntarily consented and completed baseline questionnaires since the first wave of invitations in 2001 (July 2001 to June 2003; $n = 77,047$), 2004 (Panel 2 enrolled between June 2004 and February 2006; $n = 31,110$), and 2007 (Panel 3 enrolled between June 2007 and December 2008; $n = 43,440$), resulting in a 34% cumulative baseline response rate. More than 70% of the first two panels have submitted at least one follow-up questionnaire.

Study Population

Cohort composition and survey instruments were designed in 2000. An initial random sample of active-duty, Reserve, and National Guard members from all services was constructed by the Department of Defense Manpower Data Center (DMDC) from all US military personnel serving in October 2000. The study team spent the remainder of 2000 and the first part of 2001 conducting a pilot test, which represented 1% of the original sample.^{10,11} The instrument and methods for conducting the study were further refined, and the Millennium Cohort Study officially began enrollment on July 1, 2001. The invited Millennium Cohort Study participants were randomly selected; however, oversampling of those who had been previously deployed to Bosnia, Southwest Asia, or Kosovo

(1998 to 2000), Reserve and National Guard members, and women was conducted to ensure sufficient power to detect statistical differences in smaller subgroups of the population.

Demographic and military-specific data were obtained from electronic personnel files maintained by DMDC, including sex, birth date, highest education level, marital status, race/ethnicity, deployment experience in support of wars in Iraq and Afghanistan, pay grade (rank of the service member), service component (active duty consisting of full-time military members and Reserve/National Guard who are mostly citizen soldiers with often full-time employment outside of the US military), service branch (Army, Air Force, Navy, Marine Corps, and Coast Guard), and occupation.

Questionnaire

The questionnaire was designed to assess medical outcomes and symptoms, chronic multisymptom illnesses, mental and physical health, physical activity, sleep, alcohol consumption, complementary and alternative health therapies, tobacco use, physical activity, weight change, energy supplementation, family stressors, occupational stressors, occupational exposures, deployment-specific locations and dates, deployment-specific exposures, injury, mild traumatic brain injury, duty and primary occupation, and reasons for leaving military service (Table 1).

Multiple standardized instruments are included in the questionnaire, including the posttraumatic stress disorder (PTSD) Checklist-Civilian Version¹⁴; the Patient Health Questionnaire to assess depression, panic, anxiety, eating disorders, and alcohol-related problems¹⁵⁻¹⁸; the Medical Outcomes study Short Form 36-Item Health Survey for Veterans to assess functional health¹⁹; and potential problem drinking assessed using the CAGE questionnaire.²⁰ These standardized instruments included in the questionnaire have been shown to be internally consistent and reliable as

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TABLE 1
Millennium Cohort Questionnaire; 83 Questions With 258 Items
Question Category

Demographics	
Contact information, birth year, last 4 digits of social security number, and date survey is started (6 questions)	
Marital status, education, height, and weight (5 questions)	
Active military status, and primary and secondary job codes for enlisted, and officer (3 questions)	
Separation from the military (3 questions)	
Reasons for separation from the military (1 question with 10 items)	
Behavioral	
Type of tobacco product (1 questions with 4 items)	
Smoking status (5 questions)	
Type and quantity of alcoholic beverage (9 questions)	
Alcohol abuse (1 question with 5 items; PHQ*)	
Problem drinkers (1 question with 4 items; CAGE*)	
CAM* treatments (1 question with 12 items)	
Supplement use (1 question with 3 items)	
Eating disorders (2 questions with 8 total items; PHQ*)	
Caffeine and fast food intake (2 questions)	
Strength and duration of physical activity (1 question with 3 items; NHIS*)	
Daily physical activity and inactivity (2 questions; NHANES*)	
Sleep duration (1 question)	
Occupational exposures	
Personal and environmental exposures (2 questions with 15 total items)	
Deployment-related combat exposures (1 question with 13 items)	
Location and type of deployment (3 questions)	
Anthrax vaccination (1 question with 2 items)	
Smallpox vaccination (1 question)	
Women's health	
Menstrual period, reasons for not having a menstrual period, symptoms of menstrual period, child birth, miscarriage, and trouble conceiving (1 question with 7 items)	
Mental health assessment	
DSM-IV symptoms of PTSD (1 question with 17 items; PCL-C†)	
Mental health, emotional role, social function, and vitality (5 questions with 12 total items; SF-36V†)	
Depression, panic, anxiety, risk, physical assault, and medication (7 questions with 41 total items; PHQ*)	
Stressful life events (1 question with 11 items)	
Symptoms and conditions	
Provider-diagnosed general health conditions (1 question with 41 items)	
Persistent or recurring health problems (1 question with 19 items)	
Somatoform disorder (1 question with 13 items; PHQ*)	
Physical functioning, physical role, bodily pain, and general health (7 questions with 18 total items; SF-36V†)	
Hospitalization and inability to work or perform usual activities due to illness or injury (2 questions)	
Events that caused serious injuries including head trauma, motor vehicle accident, training, and combat (2 questions)	
Open-ended question to allow for additional health information (1 question)	

*PHQ, Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Health Questionnaire; CAGE, "cut down, annoy, guilty, and eye opener"; CAM, Complementary and Alternative Medicine; NHIS, National Health Interview Survey; NHANES, National Health and Nutrition Examination Survey; SF36-V, Short-form health survey.

†SF-36V, Medical Outcomes Study, Short-Form 36-item questionnaire for Veterans; PCL-C, Posttraumatic Stress Disorder Patient Checklist, Civilian Version.

measured using Cronbach's alpha, indicating an appropriate measurement tool for this population.¹⁴

The questionnaire was designed to take between 30 minutes and 40

minutes with the ability to take it online or by hard copy mailed through the US postal service.¹⁰

There are 83 questions with multiple items that comprise the 24-page

questionnaire. Both online and paper offer the cohort member the ability to leave the questionnaire and return to where they left off. The period for follow-up assessment is 18 months.

Medical Outcomes Assessment

The Millennium Cohort questionnaire assesses 40 health professional-diagnosed conditions that include conditions such as hypertension, heart disease, emphysema, asthma, hepatitis, hearing loss, sleep apnea, cancer, depression, and PTSD.²¹ In addition to self-reported data, electronic military health data are linked to include inpatient, outpatient, pharmaceuticals, vaccination information, and mortality data (Fig. 1) (Granado et al, unpublished data).²¹⁻²⁵ Further, VA collaboration allows linking of VA health care and mortality data after service members leave military service.²⁶

Millennium Cohort Web Site

The Millennium Cohort Study Team designed and maintains a highly secure web site (www.millenniumcohort.org) capable of being accessed by Cohort members anywhere Internet access is available, enhancing the ability to provide participants with updates on the study's progress.¹⁰ In addition, the web site offers a means by which participants can contact the study team and update their contact information.^{27,28} Because of the capabilities of the web site, the study team was able to implement a bimodal approach for questionnaire submission by allowing both Web submission in addition to traditional paper submission. The additional implementation of the web site offered significant cost savings and higher quality data. Few or no differences between Cohort members submitting paper surveys when compared with those submitting via the Web have been found.²⁷

Review and Oversight

The Millennium Cohort Study has multiple reviews and structured oversight. Annual review of the

Complementary Data Sources

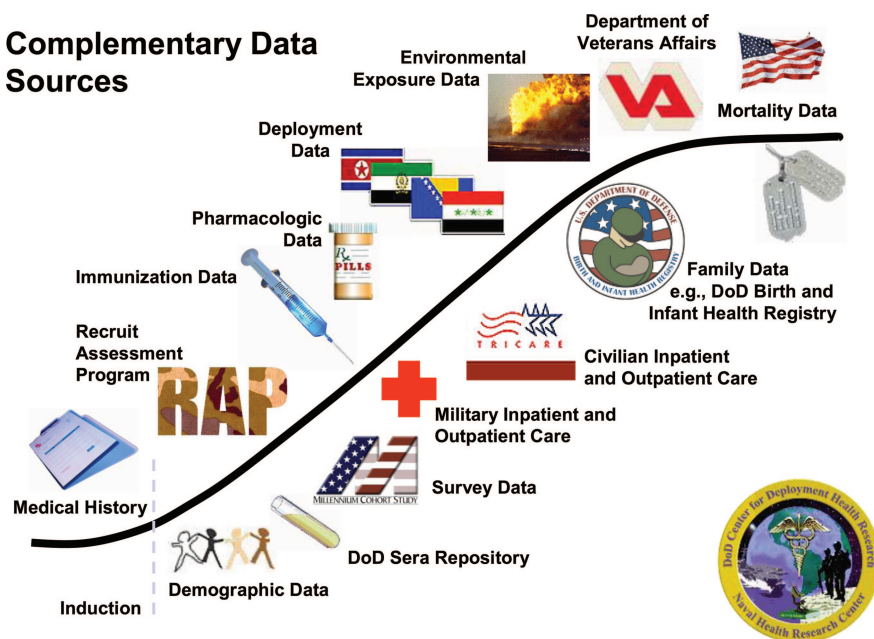


Fig. 1. The multiple complementary electronic data sources that are or that may be linked to Millennium Cohort self-reported data.

study is conducted by the Institutional Review Board at the research site, the Naval Health Research Center (Protocol NHRC.2000.0007). Moreover, regular scientific peer-review by the American Institute of Biological Sciences, DMDC review of survey content, Office of Management and Budget reviews of science, Defense Health Board review of science, and a yearly scientific steering and advisory committee meeting of leading academicians, veterans service organizations representatives, and military representatives help to guide the long-term study.¹⁰

Support

The study is funded by the Department of Defense through the US Army Medical Research Materiel Command (USAMRMC) Military Operational Medicine Research Program (MOMRP). The Millennium Cohort Study requires considerable financial and logistical support that must be projected and maintained over the lengthy period of observation. This takes a large and dedicated staff of professionals who understand the complexities of conducting a cohort study of this size and who

continually strive to find ways to make the process more efficient. The study is conducted at the Naval Health Research Center (NHRC) in San Diego by a multidisciplinary team of epidemiologists, statisticians, physicians, research assistants, and data programmers.

Exposure Metrics

Exposure assessment is important for hypothesis-driven research as well as controlling for confounding that may affect research conclusions. In health-related studies, it is important to assess and control for behavioral exposures. The Millennium Cohort survey assesses alcohol use, tobacco use, complementary and alternative therapies, body mass index, physical activity, and nutritional supplement use. It is difficult to completely assess occupational exposures and to differentiate between those occurring as a result of one's occupation and those occurring in conjunction with personal nonoccupational settings. The Millennium Cohort survey assesses personal and family stressors that include changes in residence, job changes, suffering sexual or physical assaults, and death or severe illness

of family members. In addition to assessing changes in job description through military occupational specialty codes as well as self-reported job codes, occupational exposures assessed include jobs requiring protective equipment, routine skin contact with paint and/or solvents, microwaves, and pesticides. Military-specific exposures assessed include witnessing a person's death due to war, disaster, or tragic event; witnessing instances of physical abuse; seeing dead or decomposing bodies or prisoners of war; or being exposed to or provided with countermeasures for chemical/biological/radiological (CBR) warfare agents or depleted uranium. Assessment of exposures specific to military deployment include feeling in danger of being killed, being attacked or ambushed, receiving small-arms fire, clearing homes or buildings, having an improvised explosive device explode nearby, being wounded or injured, seeing or handling human remains, knowing someone seriously injured or killed, having members in unit seriously injured or killed, and being directly responsible for death of non-combatants or enemy combatants.

Results

There are more than 150,000 consenting Millennium Cohort members who represent the US military in demographic, occupational, military, and health-related characteristics. Enrollment and follow-up cycles for the first panel have resulted in 77,047 completing the initial baseline survey (2001 to 2003), with 55,021 completing the first follow-up (2004 to 2006). Also, as originally designed, the Cohort was later augmented with 31,110 new accessions (personnel with 1 years to 3 years of service) who completed a baseline survey between 2004 and 2006, and again with >40,000 new accessions who completed a baseline survey between 2007 and 2008. More than 70% of Cohort members who submitted baseline data have submitted a follow-up questionnaire.

TABLE 2

Characteristics of Millennium Cohort Study Participants and US Military Personnel at 2008

Characteristic	Active Duty ^a Millennium Cohort Members (%)	Active Duty US Military Personnel in 2008 ^b (%)	Reserve or National Guard ^a Millennium Cohort Members (%)	Reserve or National Guard US Military Personnel in 2008 ^b (%)
Gender				
Male	69.6	85.8	65.8	83.2
Female	30.4	14.2	34.2	16.8
Age, yr				
17–24	47.8	33.9	29.9	19.3
25–34	34.8	40.8	30.3	34.3
35–44	15.1	20.8	25.0	20.1
>44	2.3	4.5	14.8	26.3
Education				
Less than high school diploma	4.5	8.8	15.8	19.6
High school diploma diploma/ equivalent	64.9	67.2	42.6	53.1
Some college	13.0	6.1	16.9	6.1
Bachelor's degree	12.3	11.9	18.1	14.9
Advanced degree	5.3	6.0	6.6	6.3
Marital status				
Single	48.6	40.5	44.8	41.1
Married	48.2	55.3	47.9	51.7
Divorced	3.2	4.2	7.3	7.2
Race/ethnicity				
White non-Hispanic	67.5	62.8	76.3	66.4
Black non-Hispanic	13.3	16.0	11.5	13.3
Asian/Pacific Islander	8.5	4.8	3.4	3.3
Hispanic	8.0	10.3	6.8	8.4
Native American	1.5	1.8	1.0	1.3
Other/unknown	1.2	4.3	1.0	7.3
Operation Iraqi Freedom/ Operation Enduring Freedom deployment status ^b				
Deployment experience	55.0	56.6	40.7	40.4
No deployment experience	45.0	43.4	59.3	59.6
Military pay grade				
Enlisted	84.6	84.2	79.1	82.5
Officer	15.4	15.8	20.9	17.5
Branch of service				
Army	34.6	37.1	59.7	54.6
Air Force	30.5	23.1	27.0	21.9
Navy/Coast Guard	22.8	26.3	10.2	14.3
Marine Corps	12.1	13.5	3.1	9.2
Occupational category				
Combat specialists	18.3	22.4	16.6	17.9
Electrical repair	10.3	8.8	6.7	5.2
Communications/intelligence	9.7	8.8	5.6	5.8
Health care specialists	10.0	8.2	12.1	7.8
Other technical	3.3	2.9	2.7	3.1
Functional support specialists	16.8	16.0	21.9	20.5
Electrical/mechanic	17.0	17.2	12.1	13.1
Craft workers	2.8	3.1	4.0	5.1
Service support	8.6	9.6	11.2	13.1
Students, trainees, other	3.2	3.0	7.1	8.4

^aCharacteristic measured at the time of baseline invitation.

^bBased on US military rosters as of March 2008 with complete demographic data.

^cDeployment experience recorded as of March 2008.

T2 Demographic data for the Cohort are presented in Table 2. For comparison purposes of the Cohort to the US military in general, a snap shot of the

US Military in 2008 is presented in Table 2 stratified by active duty and Reserve/National Guard status. At baseline, the active duty portion of

the Cohort (~60%) comprised ~70% men, 80% younger than 34 years, 70% with a high school diploma or equivalent, 50% married,

90% enlisted, 35% Army personnel, 15% combat specialists, and 10% health care specialists. At baseline, the Reserve and National Guard portion of the Cohort (~40%) comprised ~70% men, 60% younger than 34 years, 55% with a high school diploma or equivalent, 50% married, 75% enlisted, 60% Army personnel, 15% combat specialists, and 10% health care specialists. These baseline military and demographic characteristics reasonably reflect the composition of the US military in 2008. Although the Cohort is a good reflection of the composition of the US military, there are noticeable differences in the active duty Cohort members when compared with active duty in March 2008 with the Cohort comprising proportionately more women, younger, educated, single, white non-Hispanic, Air Force, and with some deployment experience in support of the wars in Iraq and Afghanistan when compared with the military in general. Moreover, there are noticeable differences in the Reserve/Guard Cohort members when compared with all Reserve/Guard in March 2008 with the Cohort comprising proportionately more women, educated, white non-Hispanic, and officers than in the general military.

Investigations have focused on establishing reliability and representativeness of Cohort data, cross-sectional prevalence studies, and prospective analyses using two data points in time. Future analyses using repeated health and exposure assessments will yield a significant and exponential increase in inferential capability (Fig. 2). To date, >50% of the 150,000 Cohort members have been deployed in support of the wars in Iraq or Afghanistan. Data analyses have been performed using SAS statistical software version 9.1 (SAS Institute, Inc., Cary, NC).

Discussion

The Millennium Cohort Study was created after lessons learned from the

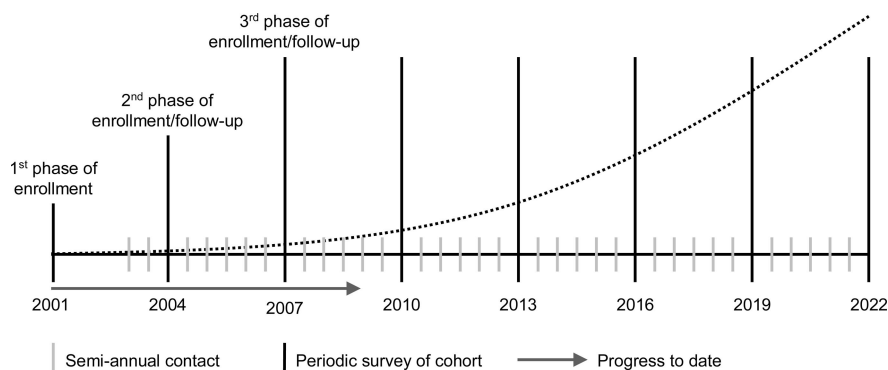


Fig. 2. The planned longitudinal design of the US DoD Millennium Cohort Study until 2022 and the potential temporal increase of research benefit.

1991 Gulf War, which made it apparent that a well-designed prospective cohort study was critical to adequately investigate long-term health consequences associated with military service. The Cohort allows for robust comparisons of deployed and nondeployed, active-duty and Reserve and National Guard members across all services. Using data from the Millennium Cohort Study, recent research has uniquely included active duty, Reserve, and National Guard members from all services and focused on comparisons of populations including deployed without reported combat exposures, deployed with reported combat exposures, and nondeployed. Prospective analyses of those deployed in support of the wars in Iraq and Afghanistan and those not deployed have answered questions regarding newly reported respiratory symptoms and conditions (Smith et al, unpublished data, 2008), hypertension,²⁹ PTSD symptoms,^{30,31} depression,³² disordered eating,³³ newly reported cigarette smoking,³⁴ and newly reported problem alcohol drinking.³⁵

Never before has such a large population-based cohort had the ability to link to a multitude of electronic data including inpatient and outpatient health care^{21,36} pharmaceutical prescriptions (Granado et al, unpublished data), vaccinations,^{22-25,37,38} the DoD Birth and Infant Health Registry,³⁹ the DoD Serum Reposi-

tory,⁴⁰ mortality while in service and post service,⁴¹ exposure data collected and maintained by the US Army Center for Health Promotion and Preventive Medicine,⁴²⁻⁴⁴ contingency/deployment data,⁴⁵ and VA health and mortality data²⁶ after separation from military service. These electronic DoD and VA data allow for the observation of a full spectrum of health exposures and outcomes and significantly strengthens the capability of this longitudinal cohort study (Fig. 1).

At baseline, the Millennium Cohort Study enrolled and consented 36% of those invited to participate in the 21-year study.¹⁰ Understanding the limitations or potential biases of this cohort is paramount to long-term inferential capabilities. Concerns over generalizability, reliability of self-reported data, and loss to follow-up are inherent in longitudinal cohort studies caused by these limitations. The Millennium Cohort study Team has made great efforts to investigate potential biases. Weights have been created and employed for the inverse of the sampling scheme as well as for the inverse of response differences with minimal differences in results.^{46,47} Analyses have shown no differential in responder health with respect to hospitalization and outpatient encounters in the year prior to enrollment, suggesting that prior health did not effect enrollment.³⁶ Reliability of reporting assessed using both test-retest analyses

and internal consistency investigation of standardized scores,¹⁴ and similar reporting in comparisons of self-report to electronic vaccination data,^{23,24} occupational data,⁴⁸ and deployment data has been established.⁴⁹ Additional analyses have shown minimal differences between participants choosing Web submission versus paper submission,²⁷ and strategies for retention are providing positive results.²⁸ Although the Millennium Cohort study Team has worked hard to maximize retention, which has resulted in a follow-up rate of >70%, analyses of response in separated and nonseparated personnel as well as potential responder bias to follow-up are ongoing.

Current areas of research include investigations differentiated by deployment focusing on diabetes, weight change, hearing loss, migraine headaches, unit cohesion, complementary and alternative medicine and health care use, complementary and alternative medicine use and mental health symptoms and diagnoses, physical activity and PTSD symptoms, professional care provider occupations and PTSD and depression symptoms, chronic multisymptom illnesses and associated comorbidities, motor vehicle accidents among deployers, and mortality.

Future strategic research plans include conducting augmented contact and focused surveys; neurocognitive testing of select subsamples of the Cohort; neuroimaging of select subsamples of the Cohort; biological sampling using blood/DNA/RNA; linking to accession data in the Recruit Assessment Program; continuing investigations of biases and loss to follow-up; longitudinal investigation of effects of multiple deployments on mental and functional health; longitudinal investigation of resolution and new onset of mental health morbidity including PTSD; longitudinal investigation of resolution and new onset of alcohol use/misuse; longitudinal evaluation of new, reuptake, or varied use of tobacco (smoking cigarettes or cigars,

or using smokeless tobacco); longitudinal investigation of mild traumatic brain injury; longitudinal investigation of respiratory conditions and illnesses; chronic sleeping deficiencies and mental symptoms; physical activity and persistence or resolution of mental health disorders; investigation of long-term chronic illnesses, such as diabetes and hypertension, and their impact on military service; chronic conjunctivitis and trachoma among deployed service members; longitudinal assessment of mortality; parental stress associated with deployment and birth-related outcomes; and family unit stress; and health effects associated with military-unique occupational exposures.

Although the cohort design offers superior inferential capability over other observational studies, there are limitations and strengths that should be discussed. Limitations to cohort studies include how generalizable the responders are to the rest of the military, self-reporting of symptoms and reporting of exposures, loss to follow-up, and rare outcomes that would not allow the statistical power to establish exposure to outcome inferences. Strengths to this cohort design include the ability to temporally investigate an exposure and health outcome, to detect outcomes with longer latency, and to ascertain symptom duration, resolution, and chronicity of the symptoms and illnesses being measured. Unique to the Millennium Cohort Study is the additional strength of being able to link these data to a wealth of DoD and VA electronic data that include personnel files, birth and infant health, inpatient and outpatient health care use, pharmaceutical use, vaccination experience, deployment experience, exposures, and mortality (Fig. 1).

Funded by the DoD through the USAMRMC MOMRP and conducted at NHRC with coinvestigators from all services and the VA, this large study symbolizes triservice and VA cooperation needed to effectively assess career-span health out-

comes now and beyond military service. The uniqueness of this study's temporal inception, which allowed launching before September 11, 2001, and the beginning of combat deployments in Afghanistan and Iraq with continued assessment, will yield answers to leadership for years to come. The sustained high operational tempo since September 2001 has been marked by significant combat operations, multiple and often lengthy deployments, and higher rates of postdeployment mental health morbidity associated with combat deployment.^{30,50,51} US fighting personnel have never been better equipped with advanced weaponry and body armor on the battlefield, nor has a better strategic long-term cohort study been implemented to answer health concerns after service members return and long after deployments conclude. PTSD, mild traumatic brain injuries (concussions), and mental health morbidity remain a significant challenge for both the service member and the medical community, potentially for years to come. The Millennium Cohort Study, currently in its eighth year, will continue to answer health concerns now and into the future.

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