Linking Exposures and Health Outcomes To a Large Population-Based Longitudinal Study: The Millennium Cohort Study

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ABSTRACT Objective: To describe current efforts and future potential for understanding long-term health of military service members by linking the Millennium Cohort Study data to exposures and health outcomes. Methods: The Millennium Cohort Study launched in 2001, before September 11 and the start of combat operations in Afghanistan and Iraq. Other substantial Department of Defense (DoD) health, personnel, and exposure databases are maintained in electronic form and may be linked by personal identifiers. Results: More than 150,000 consenting members comprise the Millennium Cohort from all services, and include active duty, Reserve, and National Guard current and past members, and represent demographic, occupational, military, and health characteristics of the U.S. military. These prospective data offer symptom assessment, behavioral health, and self-reported exposures that may complement and fill gaps in capability presented by other DoD electronic health and exposure data. Conclusions: In conjunction with Millennium Cohort survey data, prospective individual-level exposure and health outcome assessment is crucial to understand and quantify any long-term health outcomes potentially associated with unique military occupational exposures.

INTRODUCTION

The 1991 Gulf War was one of the shortest large-scale conflicts in military history. Although morbidity rates during the war because of combat as well as disease and nonbattle injuries were lower than in previous major conflicts,[1] soon after the war many veterans began reporting symptoms and illnesses they attributed to exposures during the war.[2–4] The 1990s were clouded with health concerns over environmental exposures stemming from the war prompting the Department of Veterans Affairs (DVA) to initiate the Gulf War Registry Health Examination on November 4, 1992, and the Department of Defense (DoD) to initiate the Comprehensive Clinical Evaluation Program on June 7, 1994.[5–11] These health registries gave systematic medical evaluations to over 100,000 of the 697,000 U.S. military personnel who served in the Gulf.[12] Nearly 1 billion dollars would be spent conducting research over the next decade trying to understand and answer veteran concerns.

Many studies attempted to retrospectively assess exposure and health outcomes through self-report.[13–19] These cross-sectional and retrospective self-report assessments reported concurrently with health outcomes were limited by self-selection to participate and recall of exposures and outcomes and reporting of these simultaneously. Misclassification of exposure and disease was an inescapable bias, and it was often difficult to ascertain if there were a differential or nondifferential impact on the study results. A nondifferential bias would reduce effect sizes toward the null and determine no association when one truly existed, whereas differential misclassification would affect the effect size in either direction, possibly establishing a statistically significant association when one did not truly exist. These limitations further eroded confidence in the research findings that were being reported.

In an attempt to understand exposure in an objective and prospective way, the U.S. Army Center for Health Promotion and Preventive Medicine (now the U.S. Army Public Health Command) launched a monumental exposure assessment effort soon after the end of the 1991 Gulf War. The effort was conducted to document the potential exposure of service personnel to smoke resulting from the Kuwait oil well fires set ablaze by retreating Iraqi forces.[20–22] Another objective exposure assessment, similarly as difficult, was the retrospective assessment of possible exposure to nerve agents inadvertently destroyed at the sprawling weapons depot at Khamisiyah, Iraq.[23,24] These exposure assessment efforts were large and unique in that they leveraged meteorological modeling, plume dispersion science, and troop unit location data with Geographic Information System technology to estimate potential exposure and dose at the unit level. Though they represented quite an advance in population exposure assessment, these data lacked a key element that would allow the understanding of exposure at the individual level.

Studies conducted in the 1990s utilized innovative new approaches including leveraging advanced statistical and survey methods, newly available electronic hospitalization data, and never-before conducted exposure assessment; however, significant limitations to the inferential capability of these studies remained. First and foremost, the lack of baseline health data was a significant hurdle that none of the studies could overcome. Additional gaps included a lack of hospitalization studies to assess health outcomes in Reserve and National Guard members or those members separated from military service where access to the military health care

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system was not possible; an inability to control for important health-related behaviors such as tobacco and alcohol use; exposure data were not at the individual level and were limited to Khamisiyah and the Kuwaiti oil well fire smoke assessments; electronic vaccination, pharmaceutical, and outpatient data were limited; and the survey data were limited by assessment of exposures and health outcomes many years after the war. The DoD, recognizing many of the limitations to this research, initiated a series of efforts in an attempt to establish accessible data that would be capable of answering future concerns of military members.

By the end of the 1990s, tri-service inpatient and outpatient data (both at military treatment facilities and care billed to the DoD from private providers) were being aggregated in large electronic databases; the DoD Birth and Infant Health Registry was established[25]; the DoD Serum Repository (DoDSR) was available for linkage and research[26]; personnel data, including demographic and occupational characteristics, were available; and routine collection of vaccination data began with the anthrax vaccination efforts.[27–30] Highlights of the first decade of the new millennium included a database to track DoD pharmacy transactions, a more robust contingency tracking system,[31] initiation of Pre- and Post-Deployment Health Assessment (DHA) screening,[32–34] and the launch of the largest prospective cohort study in military history, the Millennium Cohort.[35–37] This article briefly describes existing DoD data sources and summarizes the Millennium Cohort Study and the potential for linking these data.

DoD DATABASES

Defense Enrollment Eligibility Reporting System (DEERS)

DEERS is the central source for personnel information that includes determination of medical benefits eligibility, dates of service, demographics, and military occupation and location variables. In addition, DEERS includes the military's central immunization database.

Standard Inpatient Data Record (SIDR)

The SIDR contains 1 record for each inpatient encounter for care at all DoD hospitals worldwide, with up to 20 International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) discharge diagnoses. These files contain historical data dating from October 1988.

Standard Outpatient Data Record (SADR)

The SADR contains 1 record for each outpatient encounter for care at all DoD hospitals and clinics, with up to 4 ICD-9-CM diagnoses. These files contain historical data from November 1996.

TRICARE Encounter Data (TED)

Previously known as the Health Care Service Record, TED (institutional and noninstitutional) contains 1 record for each health care encounter (inpatient or outpatient) from civilian providers; care is covered by the DoD insurance system, TRICARE. These files contain historical data from October 1993.

Pharmacy Data

Mandatory reporting began in 2000 and resulted in a DoD-centralized electronic pharmaceutical dispensing database from the Pharmacy Data Transaction Service. This database captures mandatory reported data from all military medical treatment facilities worldwide, civilian retail pharmacy networks, and the TRICARE Mail Order Pharmacy network.

DoD Birth and Infant Health Registry

The DoD Birth and Infant Health Registry captures comprehensive health care data to define live births and infant health outcomes among more than 90,000 infants born to military families each year.[25] With nearly 1 million infants in this registry, there is considerable power to conduct robust research, even on the rarest birth outcomes.

Pre- and Post-Deployment Health Assessments

In response to Public Law 105-85 enacted by the U.S. Congress, the DoD established routine pre- and postdata collection on all service members before deployment and upon their return.[32] Pre-DHA and Post-DHA questionnaires, also known as Department of Defense Forms 2795 and 2796, have been used to gather these data since 1998.[33] The Post-Deployment Health Reassessment was initiated in 2006 to conduct a reassessment 6 to 9 months after returning from deployment.[34]

Recruit Assessment Program

The Recruit Assessment Program, launched in June 2001 at the Marine Corps Recruit Depot in San Diego, California, was designed to collect survey-based health and behavioral data from west coast Marine recruits at the time of service entrance.[38]

DoD Serum Repository

The DoDSR is a central archive of sera drawn from service members for medical surveillance purposes.[26] To date, there are over 50 million specimens that date back to the 1980s from more than 9 million service personnel included in the repository.

Defense Medical Surveillance System (DMSS)

The Armed Forces Health Surveillance Center (AFHSC) was established by the Deputy Secretary of Defense in 2008 to provide a central repository of DoD health surveillance data sets and programs including the DoD Global Emerging Infections Surveillance and Response System (GEIS) and the DMSS.[26] The AFHSC produces a Medical Surveillance Monthly Report (MSMR) allowing the efficient dissemination of medical

surveillance information of interest to the military public health community.

Immunization Data

Beginning in 1998 with the tri-service Anthrax Vaccine Immunization Program,[27] vaccination data have been maintained by DoD. Data include dates and location of vaccines given to military members, number of doses in the primary series, and annual booster dose information.[28–30]

Deployment Data

The Defense Manpower Data Center maintains a database for all contingency-related deployments and includes information regarding country location code, and start and end dates for each deployment.[31] Service members are identified as having deployed by being reported directly from personnel offices of the service branches or based on having received imminent danger pay, hardship duty pay, or combat zone tax exclusion benefits.

The Millennium Cohort Study

The Millennium Cohort Study was designed in the late 1990s in response to gaps in research conducted in an attempt to answer veteran and public concern regarding the1991 Gulf War.[35–37] The population-based Cohort was envisioned to collect self-reported data to complement the growing number of electronic DoD health and personnel databases. In addition, this Cohort was established to fill known gaps in research capabilities such as collecting data on Reserve and National Guard members, service members separated from military, baseline predeployment health, and behavioral health such as smoking and alcohol use that may influence health outcomes. The Cohort was constructed to prospectively assess long-term health in all branches of the U.S. Armed Forces and include active duty, Reserve, and National Guard members, and follow Cohort members while in and even after separation from military service. All participants enrolled in the study are followed and surveyed at 3-year interval periods. Currently, the Cohort is composed of approximately 150,000 members who will be resurveyed again in 2010–2011 (and every 3 years afterwards through 2021) and will include an additional enrollment panel of approximately 60,000 members and 10,000 spouses. More information on the design and conduct of this Cohort study is available in previously published articles.[35–37]

With nearly a decade of research conducted with this Cohort, deployment-related investigations of mental and physical health conditions have been completed, including major depression,[39,40] anxiety disorders,[39] post-traumatic stress disorder (PTSD),[39,41–45] eating disorders and weight change,[46] alcohol misuse,[47] cigarette smoking,[48] hypertension,[49] respiratory conditions,[50] diabetes,[51] sleep,[52] and mortality.[53] Unique to these efforts is the ability to conduct this research at a population level while including all services, active duty, Reserve, and National Guard members while serving as well as after military service.

Multiple standardized instruments are included in the questionnaire: the PTSD Checklist-Civilian Version to assess PTSD symptoms[20]; the Patient Health Questionnaire to assess depression, panic, other anxiety, eating disorders, and alcohol-related problems[54–57]; the Medical Outcomes Study Short Form 36-Item Health Survey for Veterans to assess perceived functional health (mental and physical)[58]; and potential alcohol dependence assessed using the CAGE questionnaire.[59] Standardized instruments included in the questionnaire have been found to be internally consistent and reliable using Cronbach's alpha and thus indicating an appropriate measurement tool for this population.[60]

Exposure assessment is an important component of the Millennium Cohort Study and allows for hypothesis testing as well as controlling for confounding that may distort research conclusions. In addition to medical outcome and mental health metrics, the questionnaire assesses alcohol use, tobacco use, complementary and alternative therapies, body mass index, physical activity, sleep, and dietary supplement use. Personal and family stressors are assessed including changes in residence or job, suffering sexual or physical assaults, and death or severe illness of family members, among others. Through a modest assessment of the continuum of potential occupational exposures, the questionnaire also assesses: service and post-service occupations[61]; anthrax and smallpox vaccination[62–64]; occupational exposures including assessment of jobs requiring protective equipment, routine skin contact with paint and/or solvents, microwaves, and pesticides (Table I); military-unique occupational exposures, including witnessing a

TABLE I. Self-Reported Occupational Exposures Assessment Included in the Millennium Cohort Study

Exposures in the Last 3 Years	No	Don't Know	Yes	If Yes, List Most Recent Year of Exposure
Occupational Hazards Requiring Protective Equipment, such as Respirators or Hearing Protection				
Routine Skin Contact With Paint and/or Solvent and/or Substances				
Depleted Uranium (DU)				
Microwaves (Excluding Small Microwave Ovens)				
Pesticides, including Creams, Sprays, or Uniform Treatments				
Pesticides Applied in the Environment or Around Living Facilities				
Any Exposure, Physical or Psychological, During a Military Deployment that had a Significant Impact on your Health? Please Specify:_____				

person's death because of 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 warfare agents or depleted uranium (Table II); and deployment dates and locations (Table III). On the most recent instruments, questions that ascertain specific military deployment-related exposures have been added including 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 one's unit seriously injured or killed, and being directly responsible for the death of noncombatants or enemy combatants (Table IV).

Though the Cohort began with approximately 1 person enrolling for every 3 contacted,[35,37] Cohort members stay engaged. Approximately 80% of participants who enrolled as part of the first 2 enrollment cycles have completed at least 1 follow-up survey. Representativeness of the Cohort to the entire military population has been investigated and suggests a reliable reporting Cohort that is reasonably generalizable.[31,35,37,39,44,60–66]

Linking Data

Large DoD populations with centralized data repositories allow for efficient and cost effective research approaches along with the samples sizes necessary to test study hypotheses. However, access to these data is not achieved readily as DoD data are protected because of the sensitive nature and often including Personally Identifiable Information (PII) and Protected Health Information (PHI). The actual linking of these large and complex data sets is in general, easily accomplished by linking individual identifiers across data platforms. The real-time constraints involve securing approvals for acquiring these data and linking is secondary to necessary human use and ethics approvals. Data Use Agreements, Memoranda of Understanding, and Joint Research Agreements are just a few of the potential agreements necessary to be in place before data linking. Often, researchers may save considerable time by requesting de-identified data sets, though this may not be practical in all settings.

Data available on military populations offer unique challenges but also significant opportunity to answer questions of concern to veterans and DoD. Used individually, examples of how these data sets may allow questions to be answered include: healthcare utilization by region, military treatment facility, or clinic; utilization by medical diagnostic coding; utilization of prescription drugs[67]; administration of vaccines; and demographic and occupational characteristics in the military over time. In isolation, these data sources are useful, when joined they become invaluable. When combined, these data allow construction of denominators and identification of control populations critical to conduct research of exposures and outcomes. Examples of linking and leveraging these centralized data include: investigating hospitalizations postdeployment (linking inpatient, personnel, and deployment data),[68–71] vaccine safety as measured by health care utilization postvaccination (linking vaccine, inpatient, personnel, and deployment data),[28–30,72] birth outcomes potentially associated with vaccine or deployment (linking the birth and infant health registry, vaccine, and/or deployment data),[65,73–75] hepatitis E seroprevalence and seroconversion among U.S. military service personnel deployed to endemic countries such as Afghanistan (linking personnel, deployment, and DoDSR data),[76] and other important health concerns potentially linked to military

TABLE III. Self-Reported Deployment Country and Imminent Danger Pay Assessment Included in the Millennium Cohort Study

Country Code or Sea Code Where Imminent Danger Pay, Hardship Duty Pay, or Combat Zone Tax Exclusion Benefits was Received, Within the Last 3 Years	Date Arrived (Month/Year)	Date Departed (Month/Year)

TABLE II. Self-Reported Stressful Occupational Exposures Assessment Included in the Millennium Cohort Study

Personal Exposures in the Last 3 Years (Not Including TV, Video, Movies, Computer, or Theater)	No	Don't Know	Yes	If Yes, List Most Recent Year of Exposure
Witnessing a Person's Death because of War, Disaster, or Tragic Event				
Witnessing Instances of Physical Abuse (Torture, Beating, Rape)				
Dead and/or Decomposing Bodies				
Maimed Soldiers or Civilians				
Prisoners of War or Refugees				
Chemical or Biological Warfare Agents				
Medical Countermeasures for Chemical or Biological Warfare Agent Exposure				
Alarms Necessitating Wearing of Chemical or Biological Warfare Protective Gear				

TABLE IV. Self-Reported Deployment Exposures Assessment Included in the Millennium Cohort Study

Experiences in the Last 3 Years	Never	1 Time	More Than 1 Time	If Yes, List Most Recent Year of Exposure
Feeling that You were in Great Danger of Being Killed				
Being Attacked or Ambushed				
Receiving Small Arms Fire				
Clearing/Searching Homes or Buildings				
Having an Improvised Explosive Device (IED) or Booby Trap Explode Near You				
Being Wounded or Injured				
Seeing Dead Bodies or Human Remains				
Handling or Uncovering Human Remains				
Knowing Someone Seriously Injured or Killed				
Seeing Americans who were Seriously Injured or Killed				
Having a Member of Your Unit be Seriously Injured or Killed				
Being Directly Responsible for the Death of an Enemy Combatant				
Being Directly Responsible for the Death of a Noncombatant				
Being Exposed to Smoke From Burning Trash and/or Feces				

occupational experiences. Importantly, although these data are robust in answering many questions, limitations do exist and include: unequal ascertainment by component status where Reserve and National Guard are often not represented completely in military health system data; unequal ascertainment by separation from service status where those separated often no longer have access to health care and would not be visible to researchers; potential for over estimation of cases because of rule-out diagnoses if scanning for certain diagnostic codes or categories; and differential access to care and reporting in forward deployment theaters.

Early Millennium Cohort data linkages focused on testing the reliability of self-reporting by linking to DoD electronic vaccine, healthcare, deployment, and occupation data while also linking to demographic and other occupational data to highlight differences in population reporting reliability.[31,61,63,65,66] Linking to mortality data allowed for investigation of mortality ascertainment between the National Death Index, Social Security Administration Death Master File, DoD Medical Mortality Registry, and DVA mortality data sets, and is facilitating a unique effort to investigate an 8-year prospective study of suicide in this large cohort during a period of high operational tempo.[53] Prospective Cohort data have been linked to demographic, deployment, and occupation data to understand potential short-term effects of deployment and reported symptoms. Follow-up of reported increases in hypertension and respiratory symptoms after deployment will allow for understanding transient or long-term implications of symptoms.[49,50] Follow-up of increased reporting of mental health symptoms in subsets of deploying forces will allow for an understanding of persistent, chronic, or episodic nature of the symptoms.[40,45] Linking of the many available DoD data sets to the Millennium Cohort allows for understanding of health implications of combat deployments that has not been possible before.

Currently, analyses are underway to link military health system data, deployment to bases with known open air burn pits, and Millennium Cohort Study data. This effort will be the first to investigate self-reported and ICD-9 assessed health outcomes and symptoms among service members deployed to several large bases with known burn pits while controlling for baseline health and behaviors.

DETERMINATION OF SUCCESS

The way forward for successful occupational and environmental research investigations will include real-time monitoring of service members' exposures in deployment environments that will facilitate quick identification and prevention of exposure while not limiting or hindering the military mission. Advances in biomonitoring technology will allow postexposure assessment of whether contact with the hazard or exposure resulted in significant markers of exposure or health effects and will allow for monitoring health outcomes potentially linked to the exposure. This approach requires a small logistical footprint, command support for monitoring in operational settings, and funding for personnel and equipment. The exposure monitoring equipment will have to be issued, the data collected, and the data downloaded to the DOEHRS database. Retrospective self-reported assessment of exposure is a viable option if designed in a way such that exposures and health outcomes are not collected simultaneously. New efforts should investigate the possibility of a standard exposure assessment tool that is responsive to the potentially unique set of occupational settings and exposures that the U.S. Armed Forces may encounter. This tool may be constructed to be service specific though designed with the ability to crosswalk exposure assessment across service branches. Yearly assessment and/or postdeployment assessment should be considered, and systematic data flow to a central DoD data repository should be considered. In this way, prospective and historical prospective investigations of exposure and subsequent health outcomes may be conducted while limiting simultaneous exposure and health outcome assessment.

Determining success may only be practical in retrospective assessment of what we have done collectively as a

community toward understanding the health of our service members. However, a plan for objectives to be met and priority setting should be conducted at high levels of the DoD and DVA, and those needs and priorities should be presented to DoD and DVA researchers in organized and systematic approaches. Organizational integration both between the DoD and DVA and within departments should be encouraged to more efficiently assess and leverage existing capabilities and to identify gaps. The balance of focus on short- and long-term goals should be weighed and efforts to address both should be coordinated at high levels of the DoD and DVA to effectively address prioritized objectives across the continuum of health outcomes during and after military service. It is through insightful vision of where we need to progress to, and collegiate collaboration between service branches, academia, private industry, and between the DoD and DVA that research of environmental exposures will advance to the level of offering credible answers to our service personnel.

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14. ABSTRACT

Objective: Describe current and future potential for understanding long-term health of military service members by linking the Millennium Cohort Study to exposures and health outcomes.

Methods: The Millennium Cohort Study launched in 2001, prior to September 11 and the start of deployments in Afghanistan and Iraq. Other substantial Department of Defense (DoD) health, personnel, and exposure databases are maintained in electronic databases and may be linked by personal identifiers.

Results: More than 150,000 consenting members comprise the Millennium Cohort from all services, including active duty, Reserve, and National Guard, and represent demographic, occupational, military, and health characteristics of the U.S. military. These prospective data offer symptom assessment, behavioral health, and self-reported exposures that may complement and fill gaps in capability presented by other DoD electronic health and exposure data.

Conclusions: In conjunction with Millennium Cohort survey data, prospective individual-level exposure and health outcome assessment is crucial to understanding and quantifying any long-term health outcomes potentially associated with unique military occupational exposures.

15. SUBJECT TERMS
cohort studies, military medicine, military personnel, veterans, longitudinal studies, occupational exposures

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