Considerations for Designing an Epidemiologic Study for Multiple Sclerosis and Other Neurologic Disorders in Pre and Post 9/11 Gulf War Veterans

DETAILS

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Board on the Health of Select Populations

Institute of Medicine

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COMMITTEE ON DESIGNING AN EPIDEMIOLOGIC STUDY FOR MULTIPLE SCLEROSIS AND OTHER NEUROLOGIC DISORDERS IN VETERANS OF THE PERSIAN GULF AND POST 9/11 WARS

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REVIEWERS

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the report before its release. The review of this report was overseen by **Dan G. Blazer,** Emeritus, Duke University Medical Center, and **Floyd E. Bloom,** The Scripps Research Institute. They were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

CONTENTS

ABBREVIATIONS AND ACRONYMS

AFHSC	Armed Forces Health Surveillance Center
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
DMDC	Defense Manpower Data Center
DOD	Department of Defense
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
IOM	Institute of Medicine
MS	multiple sclerosis
MSMR	Medical Surveillance Monthly Report
NewGen	National Health Study for a New Generation of US Veterans
NHS	National Health Survey of Gulf War Era Veterans and Their Families
ODD	other demyelinating disease
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OND	Operation New Dawn
OR	odds ratio
PTSD	posttraumatic stress disorder
RR	relative risk
SOT	statement of task
VA	Department of Veterans Affairs
VBA	Veterans Benefits Administration
VHA	Veterans Health Administration

BRIEF REPORT ON CONSIDERATIONS OF DESIGNING AN EPIDEMIOLOGIC STUDY FOR NEUROLOGIC DISORDERS

ABSTRACT Objective: To assess the feasibility of proceeding with a study as outlined in the committee's statement of task (SOT). Methods: Reviewed literature on burden of illnesses, specifically, multiple sclerosis, migraine, Parkinson's disease, and brain cancers; examined available data sources for suitability in executing the proposed study; scrutinized possible algorithms to assist in characterizing diseases in a study; and assessed the utility of a study based on available Department of Veterans Affairs (VA) data. Results: In examining the burden of illnesses, the committee found that the existing data suggest that Gulf War deployed veterans do not have a higher prevalence of the diseases of interest than the nondeployed Gulf War veterans, with the exception of headache and migraine. The burden of illness in the post-9/11 veterans cannot be compared to the nondeployed, as almost the entire cohort of those veterans has been deployed. Moreover, the VA survey data and administrative databases alone are inadequate for assessing the effects of deployment, as they are limited to users of VA health care, which comprise only 36% to 60% of the entire veteran population of interest. Conclusion: While technically feasible to conduct a study as outlined in the committee's SOT, the committee decided not to proceed with the study because it would be limited to using existing VA data (as stated in the VA contract with the Institute of Medicine of the National Academies of Sciences, Engineering, and Medicine), it would repeat the work of others, and it likely would not advance the knowledge significantly beyond what is already known. However, if additional data were made available, then a rigorous study likely could be conducted that advances knowledge on these issues.

INTRODUCTION

The Department of Veterans Affairs (VA) requested that the Institute of Medicine (IOM) of the National Academies of Sciences, Engineering, and Medicine conduct a study to respond to Public Law 110-389 enacted in 2008 (see Appendix A) to determine the incidence and prevalence, as well as the risk of developing multiple sclerosis (MS) and other neurologic diseases as a result of service in the 1990-1991 Persian Gulf and post 9/11 (that is, OEF/OIF/OND)[1] Global Operations theaters. Specifically, the other neurologic diseases to be

[1]Operation Enduring Freedom (OEF) is the name for the conflict in Afghanistan (October 7, 2001–December 28, 2014). Operation Iraqi Freedom (OIF) is the name of the conflict in Iraq (March 19, 2003–August 31, 2010). On September 1, 2010, Operation New Dawn (OND) became the new name of OIF, which officially ended on December 15, 2011.

considered are migraines, Parkinson's disease, and brain cancers, as well as central nervous system abnormalities that are difficult to precisely diagnose. The committee's statement of task (SOT), based on the legislation, is provided in the box below. However, the SOT is not addressed in this report, rather it responds to a requirement in the IOM's contract with the VA, which included (1) that "the committee will request data from the VA…. The data request will be for existing VA data, rather than for the collection of new data, however, the committee might want the data to be combined in a way that will produce a new data set" and (2) a clause regarding the feasibility of conducting the study, specifically: "Within 60 days of contract end date, provide status report/summary memorandum feasibility of proceeding with study."

Statement of Task

An ad hoc committee under the auspices of the Institute of Medicine will design and manage an epidemiologic study to determine the incidence and prevalence, as well as the risk (to the extent possible) of developing multiple sclerosis and other neurologic diseases as a result of service in the 1990-1991 Persian Gulf and post 9/11 Global Operations theaters. Other neurologic diseases to be considered include Parkinson's disease and brain cancers, as well as central nervous system abnormalities that are difficult to precisely diagnose. The committee will identify its data needs, request those data from the Department of Veterans Affairs, and will analyze the data. The resulting report will describe the study design, methods, and results on the neurologic outcomes of interest. The report will also include recommendations for legislative or administrative actions as deemed appropriate by the committee regarding data collection and/or follow-up related to the neurologic diseases under consideration.

APPROACH TO THE TASK

In January 2015, the IOM convened a committee of 13 experts, in the fields of neurology, epidemiology, and statistics, to address the task and the feasibility of proceeding with the study. At its first meeting in March 2015, the committee met with VA officials to learn about the burden of illness with regard to neurologic outcomes in veterans who have been deployed to the gulf region, to gain an understanding of the available data that might be useful in addressing its task, and to learn about past and ongoing efforts that have been undertaken in this area (Bossarte, 2015; Schneiderman, 2015; Wallin, 2015). The committee members examined VA utilization reports (see Appendix B) detailing the use of VA health services by Gulf War and OEF/OIF/OND veterans. Those reports detail the number of unique veterans with primary diagnoses or diagnoses in any position by *International Classification of Diseases* (ICD) codes that are obtained from veterans' medical records; they are not based on a review of patient records or a confirmation of diagnoses. The utilization reports provided the committee with a starting point for understanding the burden of illness in the veteran populations of interest, and to compare the outcomes of interest in the deployed versus the nondeployed, when available, in those veterans using VA health care. The VA representatives also discussed previous studies that have been conducted to gather information about the incidence and risk of MS in US veterans (for example, the studies by Wallin et al., 2012, 2014). The committee members also were presented with information regarding the datasets that are available through the VA Office of Public Health's Epidemiology Program. As the legislation directed VA to contract with the IOM

to conduct the study, and the contract specified using existing VA data, the committee focused its efforts on understanding VA data.

The committee conducted a literature search to identify published studies on the neurologic diseases of concern in Gulf War and OEF/OIF/OND veterans. Approximately 110 papers were obtained; all abstracts were reviewed, and the most relevant papers were read and discussed during the committee's meetings. Although the committee also was asked to examine central nervous system abnormalities that are difficult to precisely diagnose, the committee concluded that the lack of precision in characterizing such conditions made them impossible to assess.

Although technically feasible, particularly if data from multiple governmental (e.g., Centers for Disease Control and Prevention [CDC], Centers for Medicare & Medicaid Services [CMS], and Department of Defense [DOD]) and private sources were available, the committee decided not to go forward with designing an epidemiologic study using only the VA resources available to them. If the committee were to use the same datasets and surveys that the VA and other researchers have already used to determine the incidence and the prevalence of the neurologic conditions of interest, the committee would not advance the knowledge significantly beyond what is currently known. The remainder of this report will detail the reasons for that decision. It begins with a discussion of the burden of the specified neurologic illnesses in the Gulf War and OEF/OIF/OND veteran populations; it is followed by a discussion of how to identify cases from the VA data sources that would be available to the committee, the challenges and limitations of using those data, including the specific challenges of studying the neurologic outcomes of concern. Finally, the committee provides a summary of its findings and concluding remarks.

BURDEN OF ILLNESS

This section describes findings from VA utilization reports, Armed Forces Health Surveillance Center (AFHSC) reports, and studies of neurologic outcomes (specifically, MS, migraine, Parkinson's disease, and brain cancers) that have been conducted in Gulf War and OEF/OIF/OND veterans. The information in this section provides an overview of the burden of illnesses in the deployed veterans compared with the nondeployed or those deployed elsewhere, when available. This section is not meant to be an exhaustive search of all studies conducted in Gulf War and OIF/OEF/OND veterans, but to highlight many of the studies that have been conducted using VA and other data. Appendix C contains a summary table of the selected reports and studies that are cited in this section.

Multiple Sclerosis

MS is a chronic inflammatory, demyelinating disease of the central nervous system with an unknown etiology. According to the National Institute of Neurological Disorders and Stroke of the National Institutes of Health, MS is the most common disabling neurologic disease of young adults. It most often appears in individuals between the ages of 20 and 40 years old with an unpredictable course. Some individuals will have little disability, while others will have a course leading to increased disability over time (NIH, 2015c). Although MS can cause severe disability, it is only rarely fatal. In the United States, the number of people with MS is estimated to be about 400,000, with approximately 10,000 new cases diagnosed annually; however, that

estimate of MS prevalence was calculated in 2002 by the National MS Society using age-specific rates applied to various age subgroups using Census 2000 data. Overall, the incidence of MS in women is two to three times that in men (National MS Society, 2015).

VA utilization reports (see Appendix B) were reviewed; data gathered between October 1, 2001, and September 30, 2013, found that 286,995 veterans (46%), of the 621,901 veterans who deployed in the 1990-1991 Gulf War, used VA health care at least once (VA, 2014a). Over that same time period, 269,635 nondeployed Gulf War veterans (36%) used VA health care services at least once out of a total of 746,247 nondeployed (VA, 2014b). Of those deployed and nondeployed veterans using VA health care services, a primary diagnostic code of MS, entered by any provider during an inpatient or outpatient encounter, was listed for 1,040 deployed and 1,089 nondeployed veterans; however, diagnosis of MS was not confirmed. The odds of having at least one primary diagnostic code of MS is statistically significantly lower for deployed 1990-1991 Gulf War veterans compared with nondeployed veterans (odds ratio [OR] = 0.90, 95% confidence interval [CI]: 0.82-0.98) (VA, 2014a,b).

The VA presented similar information, in its utilization reports, for deployed veterans of OEF/OIF/OND who used VA health care at least once between October 1, 2001, and September 30, 2014. Information on nondeployed OEF/OIF/OND veterans is not available. Within that time period, 1,866,128 veterans separated from the military and 1,126,173 (60%) received VA health care. Of the VA health care users, 1,529 had a primary diagnosis of MS (VA, 2015).

The AFHSC issues a monthly and an annual summary of morbidity outcomes attributable to various illnesses and injuries. The Medical Surveillance Monthly Report (MSMR) provides monthly estimates of the incidence, distribution, impact, and trends of health conditions among service members. The surveillance population consists of all individuals who served on active duty within any branch from January 1 to December 31 of a given year. All medical encounters (both inpatient and outpatient) are included and the primary diagnostic code that is assigned at each encounter is used to summarize categories of conditions (see Appendix B). DOD monitors MS activity in service members and, during the period January 2000 through December 2009, found the incidence rates to be stable over the 10 years of surveillance. Cases[2] were identified by using primary diagnostic ICD-9-CM codes[3] of 340 and 341. The overall incidence rate was 12.9 per 100,000 person-years. The crude incidence rate was 3.3 times higher in females (32.0 per 100,000 person-years) than males (9.6 per 100,000 person-years) (MSMR, 2011). Additionally, in its annual summary of morbidity for all individuals who served on active duty within any branch from January 1 to December 31, 2014, the AFHSC reported that 3,288 medical encounters (both inpatient and outpatient) were attributed to a primary diagnosis of MS affecting 665 unique individuals (MSMR, 2015).

Because concern has been raised that US veterans of the 1990-1991 Gulf War might be at increased risk for MS, the VA assembled an incident cohort of MS cases. Wallin et al. (2012) characterized a new nationwide incident cohort of MS among US veterans. The methods were similar to the only other comprehensive epidemiologic study of MS in US veterans conducted in

[2]A case was defined as an individual with a single inpatient diagnosis of MS, two outpatient encounters with diagnoses of MS, or an inpatient or outpatient encounter with other demyelination diseases of the nervous system, followed by an outpatient encounter with MS.

[3]The *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) is based on the World Health Organization's *International Classification of Diseases, Ninth Revision* (ICD-9). ICD-9-CM is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

the 1970s (Kurtzke et al., 1979). VA medical records and benefits data were linked with DOD data to identify all veterans who had applied for and were evaluated for a service-connection for MS, and had active duty service between 1990 and 2007. The authors also identified individuals who had applied for service connection for clinically isolated syndrome, including optic neuritis and transverse myelitis. Denominators for incidence rates came from DOD databases and active-duty population data were obtained for each year (summing the active-duty forces for each year over 18 years provided the total person-years). The 2005 McDonald criteria[4] were used to validate MS cases. Wallin et al. (2012) linked the VA records with the Gulf War database of all active-duty service members from DOD and identified a total of 2,691 MS or clinically isolated syndrome cases (2,288 definite MS, 190 possible MS, 207 clinically isolated syndrome, and 6 cases with a rare MS-like illness—neuromyelitis optica).

Wallin et al. (2014) then evaluated the relative risk (RR) of developing MS and other central nervous system demyelinating diseases (ODDs) in deployed Gulf War veterans using the same incident cohort previously described. Cases of MS and ODD (predominantly clinically isolated syndrome) were matched to a DOD database of all active-duty personnel (to compare the incidence of MS in those who were and were not deployed). All cases, evaluated for service connection to MS or clinically isolated syndrome, were reviewed by trained research abstractors and relevant demographic, clinical, and environmental exposure variables were recorded. The diagnoses of MS were reviewed and confirmed by one of the study's neurologists. Additionally, all service connected cases had initial and ongoing demographic and medical data. A total of 1,841 incident cases of MS and ODD were identified: 387 cases among the 696,118 deployed and 1,454 cases among the 1,786,215 nondeployed veterans. The RR of MS was statistically significantly lower in the deployed compared with the nondeployed (RR = 0.69, 95% CI: 0.61-0.78). No differences in the RRs of MS were seen among deployed women or non-whites compared with the respective nondeployed groups. Findings indicate that, after 18 years of follow-up, deployment to the Gulf War was not associated with an increased risk of developing MS.

Barth et al. (2009) compared neurologic mortality rates through 2004 in the entire deployed cohort of 621,902 veterans who served in the Gulf War between August 1, 1990, and March 1, 1991, with 746,248 veterans who served in the military during this time period but were not deployed to the Gulf War. Records from the VA Beneficiary Identification Records Locator Subsystem, a database consisting of all veterans eligible for VA benefits, and the Social Security Administration's Death Master File were examined. Experts who were blinded to the deployment status of veterans reviewed the death certificates and medical records and classified them using the McDonald criteria (Polman et al., 2005). A total of 19 deaths due to MS were identified; 6 in the deployed group and 13 in the nondeployed group. The adjusted rate ratio for MS mortality did not suggest an increased risk (rate ratio = 0.61, 95% CI 0.23-1.63). Thus, the authors found no evidence of increased risk of death from MS associated with Gulf War service.

Migraines

About 12% of the US population has had a migraine headache, which is a recurring attack of moderate to severe pain. The pain is throbbing or pulsing and is often on one side of the

[4]The 2005 McDonald criteria (updated from 2001) are a set of diagnostic criteria for MS that incorporate the clinical characteristics alone or in combination with magnetic resonance imaging features.

head. During migraines people are very sensitive to light and sound; they may also experience nausea and vomiting. Migraines are more common in women than men (NIH, 2015b). There is no diagnostic test for migraines and diagnosis is based on applying diagnostic criteria that rely on clinical symptoms. Migraines are often triggered by foods, smells, and stress and are more common in people who have experienced head injuries or have psychiatric comorbidities. Migraines are often relieved by non-pharmacologic or over-the-counter treatments and medical attention is often not sought. While migraine-specific medications exist, they are used primarily in patients with frequent and severe headaches.

VA utilization reports were reviewed; data gathered between October 1, 2001, and September 30, 2013, found that 286,995 veterans (46%) of the 621,901 veterans who deployed in the 1990-1991 Gulf War used VA health care at least once (VA, 2014a). Over that same time period, 269,635 nondeployed Gulf War veterans (36%) used VA health care services out of a total of 746,247 nondeployed (VA, 2014b). Of those deployed and nondeployed veterans using VA health care services, a primary diagnostic code of migraine (ICD-9-CM: 346), entered by any provider during an inpatient or outpatient encounter, was listed for 16,327 deployed and 14,115 nondeployed veterans; however, diagnosis of migraine was not confirmed. The odds of having a primary diagnosis of migraine were statistically significantly higher for deployed veterans compared with nondeployed veterans (OR = 1.09, 95% CI: 1.07-1.12) (VA 2014a,b).

The VA utilization data present similar information for deployed veterans of OEF/OIF/OND who used VA health care at least once between October 1, 2001, and September 30, 2014. Information on nondeployed OEF/OIF/OND veterans is not available. Within that time period, 1,866,128 veterans separated from the military and 1,126,173 (60%) received VA health care. Of the VA health care users, 58,045 had a primary diagnosis of migraine over the 13-year period (VA, 2015). Although the number of primary diagnoses of migraine is greater in the OEF/OIF/OND deployed veterans than the Gulf War veterans, the period prevalence of migraine is lower (0.0515) than the period prevalences for Gulf War deployed and nondeployed veterans (0.0569 and 0.0523, respectively) (VA, 2014a,b, 2015).

In its annual summary of morbidity for all individuals who served on active duty within any branch from January 1 to December 31, 2014, the AFHSC reported that 164,229 medical encounters (both inpatient and outpatient) were attributed to a primary diagnosis of headache, affecting 74,023 unique individuals (MSMR, 2015). No additional information was provided, such as whether those headaches were migraines or if they might be related to traumatic brain injury.

Kang et al. (2000) used survey data collected from the National Health Survey of Gulf War Era Veterans and Their Families (NHS) (see Appendix B), to report outcomes related to recurrent headaches and migraines experienced in the past 12 months among 1990-1991 Gulf War veterans. Self-reported responses were used to calculate weighted estimates of population rates for these conditions among Gulf War deployed and Gulf War era veterans.[5] Migraines were reported for 16.5% of deployed and 9.3% of the era veterans and recurring headaches were reported for 32.6% of deployed and 14.9% of the era veterans. Gulf War deployed veterans also reported more mild and severe "persistent or recurring problems with any headaches" in the past 12 months compared with the Gulf War era veterans. Potential confounding information, such as time of onset (before, during, or after the Gulf War) or occurrence of head trauma, was not included.

[5]Era veterans are defined as those veterans who did not deploy or who deployed elsewhere during the study period.

Further examination of the population prevalence proportions for 48 selected symptoms indicate that of the 54% of deployed Gulf War veterans reporting headaches, 40% of them were mild and 14% were reported as severe, whereas in the era veterans 37% reported headaches and of those 28% reported that their headaches were mild and 9% reported that their headaches were severe. Gulf War veterans self-report a higher prevalence of numerous symptoms, including headache and migraine than their military peers (Doebbeling et al., 2000; Haley and Kurt, 1997; Kelsall et al., 2004; Pierce, 1997; Unwin et al., 1999).

Jankosky et al. (2011) examined headache disorders in the Millennium Cohort Study.[6] The study characterized migraine and other headache disorders to assess the temporal association between deployment and combat exposure. The study analyzed data from 38,631 participants who had completed both baseline and follow-up questionnaires and were assessed for migraine and new onset headache disorder. Migraine and headache history were assessed via three questions on the follow-up questionnaire (the same three questions were asked on the VA surveys described on page 32). Combat-deployed service members had statistically significantly higher adjusted odds of new-onset headache disorder than nondeployed (OR = 1.72, 95% CI 1.55-1.90 for men; OR = 1.84, 95% CI 1.55-2.18 for women). Those deployed without combat did not have statistically significantly different adjusted odds of new onset headaches compared to the nondeployed (OR = 1.07, 95% CI 0.95-1.21 for men; OR = 0.96, 95% CI 0.80-1.14 for women). Thus, findings indicate that deployed personnel with reported combat exposure are a high-risk group for new-onset headache disorders.

Theeler and Erickson (2012) conducted a series of studies to estimate the prevalence and impact of migraine headaches in OEF and OIF soldiers. Findings indicate that headaches, in particular migraine headaches, are a common affliction in US service men and women returning from deployment to OEF and OIF. Exposure to blasts and sustaining a concussion might be important contributors to the increased prevalence of headaches in those deployed. Concussions, often a result of blast exposure, occur in approximately 20% of the deployed.

A study to assess the prevalence and impact of migraine in US Army soldiers deployed to OIF was conducted by Theeler et al. (2008). A US Army brigade was given a self-administered headache questionnaire within 10 days of returning from a 1 year combat tour in Iraq. Those who screened positive for migraine were surveyed again by phone 3 months after their return from Iraq. Results indicate that 19% of soldiers screened positive for migraine and 17% for possible migraine on return from deployment.

A study was conducted by Theeler et al. (2010) to determine the prevalence, characteristics, impact, and treatment patterns of headaches after concussion in soldiers returning from Iraq or Afghanistan. Findings indicate that more than one in three returning military personnel who sustained a deployment-related concussion have posttraumatic headaches. The predominant headache type precipitated by a concussion during deployment was classified as migraine (58%).

Theeler et al. (2012) conducted a study to determine the prevalence, characteristics, and factors associated with chronic daily headache in US soldiers after deployment-related concussion. This cross-sectional, questionnaire-based study was conducted using 978 US

[6]The Millennium Cohort Study is a 21-year longitudinal study that began in 2001 prior to the operations in Iraq and Afghanistan. A random sample of 256,400 service members of the 2.2 million total serving as of October 1, 2000, were invited to participate in the baseline cohort from 2001 to 2003. Women were oversampled and comprised about 25% of the study population. Approximately 77,000 completed the baseline questionnaire for a response rate of 36% (Ryan et al., 2007).

soldiers who screened positive for deployment-related concussion upon return from Iraq or Afghanistan. Approximately 20% of the soldiers who had a history of deployment-related concussion met criteria for chronic daily headache and 78% had episodic headache. The prevalence of chronic daily headache in soldiers returning from OEF or OIF is four to five times higher than that seen in the general US population.

The increased prevalence of migraine might be due in part to the well-known associations between migraine and posttraumatic stress disorder (PTSD) (Buse et al., 2013) and migraine and head trauma (D'Onofrio et al., 2014). Because of the prevalence of PTSD and head trauma in deployed service members compared with nondeployed service members, any meaningful analysis of migraine would have to consider PTSD and head trauma.

Parkinson's Disease

There are four primary clinical features of Parkinson's disease: resting tremor consisting of involuntary shaking in hands, arms, legs, jaw, and face; rigidity or stiffness of the limbs and trunk; bradykinesia or slowness of movement; and postural instability or impaired balance and gait. The signs of Parkinson's disease are typically asymmetric involving predominantly one side of the body. Early symptoms of Parkinson's disease are subtle and usually emerge gradually. As symptoms and signs become more advanced, patients may have difficulty walking, talking, or completing other simple tasks. Cognitive impairment and dementia may develop as Parkinson's disease progresses. The average age of Parkinson's disease onset is about 60 years (older than either the 1990-1991 Gulf War or OEF/OIF/OND cohorts) and men are more commonly affected than women. Diagnosis is based on medical history, neurologic examination, and the exclusion of other conditions (NIH, 2015d).

According to VA utilization data between October 1, 2001, and September 30, 2013, 286,995 veterans (46%) of the total 621,901 veterans who deployed in the 1990-1991 Gulf War used VA health care at least once (VA, 2014a). Over the same time period, 269,635 (36%) of a total of 746,247 Gulf War nondeployed veterans used VA health care services at least once (VA, 2014b). Of those deployed and nondeployed veterans using VA health care services, a primary diagnostic code of Parkinson's disease or paralysis agitans (ICD-9-CM: 332.0), entered by any provider during an inpatient or outpatient encounter, was listed for 403 deployed and 487 nondeployed veterans; however, a diagnosis of Parkinson's disease was not confirmed. The odds of having a primary diagnosis of Parkinson's disease or paralysis agitans were statistically significantly lower for Gulf War deployed veterans compared with nondeployed veterans (OR = 0.78, 95% CI: 0.68-0.89) (VA, 2014a,b).

VA utilization data for deployed veterans of OEF/OIF/OND who used VA health care at least once between October 1, 2001, and September 30, 2014, demonstrate that within that time period, 1,866,128 veterans separated from the military, and 1,126,173 (60%) received VA health care. Of the VA health care users, 332 had a primary diagnosis of Parkinson's disease over the 13-year period; however, diagnoses were not confirmed (VA, 2015). Information on nondeployed OEF/OIF/OND veterans is not available.

In its annual summary of morbidity for all individuals who served on active duty within any branch from January 1 to December 31, 2014, the AFHSC reported that 249 medical encounters (both inpatient and outpatient) were attributed to a primary diagnosis of Parkinson's disease, affecting 59 unique individuals (MSMR, 2015).

Barth et al. (2009) compared mortality rates from neurologic diseases, including Parkinson's disease, between May 1991 and December 2004 in 621,902 deployed and 746,248

nondeployed Gulf War veterans. Few deaths were attributed specifically to Parkinson's disease; there were no cases among female veterans in either group, but there were three deaths in deployed male veterans and eight in nondeployed male veterans. The adjusted mortality rate ratio for Parkinson's disease was 0.71 (95% CI: 0.17-2.99).

Brain Cancers

A brain tumor is a growth of abnormal cells in the tissues of the brain. Brain tumors can be benign or malignant, but even benign tumors can cause serious impairment and disability as they expand within the closed confines of the skull. Some brain tumors are primary (i.e., they start in the brain), while others represent metastasis. Some of the most common symptoms of brain cancer are headaches; nausea and vomiting; changes in the ability to talk, hear, or see; problems with strength, sensation, balance, or walking; problems with thinking or memory; feeling weak or sleepy; changes in mood or behavior; or seizures (NIH, 2015a).

According to VA utilization data, between October 1, 2001, and September 30, 2013, 286,995 veterans (46%) of the total 621,901 veterans who deployed in the 1990-1991 Gulf War used VA health care at least once (VA, 2014a). Over this same time period, 269,635 (36%) of a total of 746,247 Gulf War nondeployed veterans used VA health care services (VA, 2014b). Of those deployed and nondeployed Gulf War veterans using VA health care services, a primary diagnostic code of malignant neoplasm of the brain (ICD-9-CM: 191), entered by any provider during an inpatient or outpatient encounter, was listed for 342 deployed and 332 nondeployed veterans. The crude odds of having a primary diagnosis of malignant brain cancer were not statistically different for deployed compared with nondeployed Gulf War veterans (OR = 0.97, 95% CI: 0.83-1.13) (VA, 2014a,b).

The VA utilization report contained similar information for deployed veterans of OEF/OIF/OND who used VA health care at least once between October 1, 2001, and September 30, 2014. Information on nondeployed OEF/OIF/OND veterans is not available. Within that time period, 1,866,128 veterans separated from the military and 1,126,173 (60%) received VA health care. Of the VA health care users, 458 had a primary diagnosis of malignant neoplasm of the brain over the 13-year period (VA, 2015). Diagnoses were not confirmed.

In its annual summary of morbidity for all individuals who served on active duty within any branch from January 1 to December 31, 2014, the AFHSC reported that 2,418 medical encounters (both inpatient and outpatient) were attributed to a primary diagnosis of malignant neoplasm of the brain, affecting 206 unique individuals (MSMR, 2015).

Barth et al. (2009) conducted a study focusing on long-term mortality from neurologic disorders, including brain cancer in the 621,902 veterans who served in the 1990-1991 Gulf War and the 746,248 nondeployed Gulf War veterans. Follow-up began with the date the veteran left the Gulf War theater or May 1, 1991, and ended with the date of death or December 31, 2004. There were 144 cases of brain cancer in the deployed and 228 cases in the nondeployed veterans. Adjusted mortality rate ratios of deployed and era veterans were not statistically significant for brain cancer (rate ratio = 0.90, 95% CI: 0.73-1.1). The authors concluded that the risk of death due to brain cancer was not associated with Gulf War service.

A study was conducted by Young et al. (2010) that reviewed files obtained from the Defense Manpower Data Center (DMDC). The files included data for 621,902 veterans who were deployed to the Gulf War during August 2, 1990, to March 1, 1991, and 746,248 Gulf War era veterans. Identification of veterans who received a cancer diagnosis between 1991 and 2006 was accomplished by linking the DMDC dataset with 28 state cancer registries and the VA

Central Cancer Registry. The authors used logistic regression and proportional incidence ratios, which were adjusted for demographic and military characteristics, and were calculated by comparing the proportion of specific cancer among all cancers in the Gulf War veterans to the proportion of that specific cancer among all cancers in the Gulf War era veterans. The study did not find an excess proportion of brain cancer cases among deployed compared with era veterans. The number of brain cancers in the Gulf War deployed veterans was 278 and 410 in era veterans. The proportional incidence ratio (derived from a logistic regression model controlling for sex, diagnosis age, diagnosis age squared, diagnosis year, race, branch of service, unit type, and registry group number) comparing cases of brain cancer in deployed versus era Gulf War veterans was 0.86 (95% CI: 0.73-1.01). The overall findings are consistent with other studies that showed no additional overall risk of cancer among Gulf War veterans.

Zullig et al. (2012) examined cancer incidence among patients in the VA health care system. The authors noted that approximately 40,000 incident cancers are reported in the VA Central Cancer Registry annually, which represent about 3% of all US cancers. In 2007, the five most frequently diagnosed cancers among all VA cancer patients were prostate (31.8%), lung/bronchus (18.8%), colon/rectum (8.6%), urinary bladder (3.6%), and skin melanomas (3.4%). Incident brain cancers represented 0.7% (264 cases) of all cancers in both sexes.

CASE ASCERTAINMENT FROM ADMINISTRATIVE DATABASES

The committee considered how it might identify cases of the neurologic diseases named in the legislation using VA administrative data. Identifying cases for MS or Parkinson's disease is often difficult as no definitive diagnostic tests exist; instead, a diagnosis is made on clinical grounds and ruling out other conditions. Typically a diagnosis is entered into medical records using ICD-9-CM codes for the conditions of interest. However, several studies (discussed in this section) have shown that using a single instance of an ICD-9-CM code in a medical record does not accurately identify the number of true cases of the condition of interest (Culpepper et al., 2006; Kolodner et al., 2004; Noyes et al., 2007; Swarztrauber et al., 2005; Szumski and Cheng, 2009). Limitations of using ICD-9-CM codes alone to identify cases include coding errors (such as clerical errors, misuse, or omissions), inaccurate diagnoses, and assigning codes prematurely or for uncertain diagnoses (Szumski and Cheng, 2009). Swarztrauber et al. (2005) posited that ICD-9-CM codes, specifically for conditions that are rare or difficult to diagnose like Parkinson's disease, might have low accuracy within the VA databases because of frequent changes in ICD-9-CM code definitions within clinics or programs that are newly developed or purposely changing the application of different parkinsonism codes over time. Thus, the committee was interested in exploring the use of validated algorithms to identify cases of MS, migraine, Parkinson's disease, and brain cancer.

Using Validated Algorithms and Other Methods for Identifying Cases

Validated algorithms and other methods (e.g., mortality studies), discussed below, have been developed to identify true cases of MS, Parkinson's disease, and brain cancer using VA administrative data. Identifying true cases of MS, migraines, Parkinson's disease, or brain cancer with a high degree of precision requires different approaches due to inherent differences in the nature and frequency of those illnesses. In addition, methods that accurately identify true cases suitable for estimating prevalence may not be adequate for identifying disease onset required to

define incident cases, with the exception of malignant brain cancer. Validated algorithms using VA administrative data combined with pharmacy data, particularly when provider level information is incorporated, can identify prevalent MS and Parkinson's disease cases with a high degree of specificity. Sensitivity of the algorithms is not clear as they were designed primarily to identify non-cases.

Multiple Sclerosis

Because an ICD-9-CM code of 340 in a VA medical record can be used to indicate suspected MS, an evaluation to rule out MS, or clinically definite MS, Culpepper et al. (2006) developed an algorithm to reliably eliminate non-MS cases that received at least one MS diagnostic code during an encounter or MS specific prescription using VA medical records, service-connection records, and pharmacy data. A statistical algorithm was developed that classified cases of MS based on frequency of health care encounters (an average of at least one per year) with primary diagnostic codes of 340, and service-connection status for MS and/or use of a prescription drug specific to MS. Chart review of 2.6% of the sample was used as the gold standard for classifying MS status (MS or possible; definitely not MS; unknown, not enough data to determine). When unknown cases were included in the analysis that compared chart review to the applied algorithm, sensitivity was 93%, specificity was 90%, positive predictive value was 88%, and negative predictive value was 94%.

This algorithm might underestimate the true prevalence of MS as it does not take into account missed diagnosis of MS cases or because the veteran did not seek care at the VA during the study period. Furthermore, the algorithm assumes that everyone with MS will eventually have an MS code, but that is only true if the duration of follow-up exceeds 5-10 years.

Migraine

Kolodner et al. (2004) developed an algorithm using pharmacy and medical claims data to identify persons who experience migraines. Although the algorithm was validated using records from a managed care organization, the fields most strongly associated with migraine case status are also collected in patient health records and VA administrative databases. A sample of 8,579 eligible enrollees (between the ages of 18 and 55, continuously enrolled in the health plan for 24 months, and had at least one medical encounter in a 12-month period) completed a telephone interview that assessed headache types, characteristics, and features, and were subsequently assigned a diagnosis of migraine headache if they met the criteria using the algorithm developed by the International Headache Society (1998).[7] That algorithm was used as the gold standard and persons meeting those criteria were considered cases. Claims for a migraine-specific drug, gender, and a claims-based headache diagnosis were strongly predictive of migraine case status. Relying on the diagnostic code for migraine headache alone results in most of the migraine cases being missed (sensitivity of 18.6%). Thus, a combination of medical and pharmacy claims' variables available from administrative data and validated using records from a managed care organization can be used to identify many cases of migraine that would otherwise be missed.

The gold standard of migraine diagnosis relies on clinical interview and questions about migraines with and without aura. Martin et al. (2005) developed an abbreviated version of the

[7]The International Headache Society migraine algorithm interview had been validated previously in the United States and had a sensitivity of 85% and a specificity of 97% (Stewart et al., 1999).

diagnostic criteria that are able to accurately identify cases of migraine; however, it was not tested or validated using administrative data, but instead relied on clinical interview questions. The study sample consisted of 1,524 headache clinic patients, private practice neurology patients, college students, and community-based patients. Individual predictor variables were selected that covered all the diagnostic criteria questions and single and multivariate models were tested to determine which single predictor or combination was optimal, defined as positive likelihood ratios of >4.5 and negative likelihood ratios of <0.25. The only single predictor meeting those criteria was nausea (positive likelihood ratio of 4.8, negative likelihood ratio of 0.23, sensitivity of 81% and specificity of 83%). Two three-variable models also optimized detection of migraine. The first model was a combination of nausea/photophobia/pulsating (positive likelihood ratio of 6.7, negative likelihood ratio of 0.23, positive predictive value of 93%, and negative predictive value of 71%). The second model was a combination of nausea/photophobia/worsening with physical activity (positive likelihood ratio of 5.9, negative likelihood ratio of 0.21, positive predictive value of 91%, and negative predictive value of 74%). The authors concluded that any of those three models can be used to effectively predict migraine in diverse clinical settings, but they should be applied only after secondary headache disorders are excluded. Those results are consistent with a validated three-question screen for migraines (positive predictive value of 93% and 98% for two or three positive responses, respectively) that takes into account nausea, limited activities, and aversion to light when an individual experiences a headache (Lipton et al., 2003).

Parkinson's Disease

As previously noted, relying on ICD-9-CM codes to identify true cases of Parkinson's disease in administrative databases is problematic, in part because there is no single diagnostic test for Parkinson's disease. Szumski and Cheng (2009) developed and compared several algorithms to identify Parkinson's disease and possible Parkinson's disease cases in the VA. The authors identified cases with assigned diagnostic ICD-9-CM code of 332.0 (paralysis agitans) in any position in VA medical record based on the number of clinic visits with that code applied, whether codes were assigned from a movement disorder specialty clinic visit, and/or prescriptions for Parkinson's disease–related medications. Standardized chart review by a nurse abstractor was used as the gold standard for classifying Parkinson's disease status (Parkinson's disease, possible Parkinson's disease, not Parkinson's disease) in the 577 veterans who had at least one instance of an assigned diagnostic code of 332.0 over a 3-year period at one large VA system. Multiple algorithms were applied and compared on sensitivity, specificity, positive predictive value, negative predictive value, and simple agreement with the gold standard of chart review. For the algorithm in which the diagnostic code for Parkinson's disease was present at least twice in the record, and weighted according to code assignment at a movement disorders, general neurology, or any other clinic, sensitivity was 87.4%, specificity was 45.4%, positive predictive value was 83.2%, negative predictive value was 53.8%, and agreement with chart review was 77.1%. When the presence of a Parkinson's disease prescription was added to this algorithm, sensitivity decreased to 77.1%, specificity increased to 68.1%, positive predictive value increased to 88.2%, and negative predictive value decreased to 49%. These algorithms yielded improved parameters over using a single occurrence of a Parkinson's disease diagnostic code in the medical record.

Swarztrauber et al. (2005) also examined VA administrative databases for pharmacy and inpatient and outpatient medical records (but used a different sample of veterans than Szumski

and Cheng, 2009) to create an algorithm to accurately identify parkinsonism (including both idiopathic Parkinson's disease and secondary parkinsonism) cases. Medical record abstraction of a subset of records was used to determine the gold standard diagnoses. Using a combination of three parkinsonism ICD-9-CM codes alone (332.0, 332.1, 333.0) resulted in a low sensitivity (18.7%) but high specificity (99.9%) and fair positive predictive value (81%) for identifying true cases of parkinsonism. Pharmacy data had higher sensitivity for detecting cases of parkinsonism than ICD-9-CM codes alone, but adding parkinsonism medications to the ICD-9-CM codes resulted in even greater sensitivity (37.9%), high specificity (99.6%), but positive predictive value was 60.4%. Of most relevance for the committee is that an ICD-9-CM code of 332.0 did not accurately distinguish idiopathic Parkinson's disease and other causes or phenotypic variants of parkinsonism. Other algorithms have been developed to identify cases of Parkinson-like features, including idiopathic Parkinson's disease, using Medicare fee-for-service claims data (Noyes et al., 2007). However, those algorithms do not distinguish between Parkinson-related disorders and idiopathic Parkinson's disease.

Brain Cancer

Mortality studies are useful in studying malignant brain cancers because these types of cancers are typically fatal (5-year survival is 33%) (NCI, 2015). Mortality studies among 1990-1991 US Gulf War veterans have been conducted with periodic follow-up (Barth et al., 2009; Bullman et al., 2005). In these studies, the entire cohort of 621,902 Gulf War deployed veterans and a stratified random sample of 746,248 era veterans—those who had served in the active duty, reserves, or National Guard during the same time period but who were not deployed to the combat theater—were followed beginning May 1, 1991, until death or December 31, 2000 (Bullman et al., 2005), or December 31, 2004 (Barth al., 2009). Both of those studies performed a subsequent analysis using a subset of deployed veterans thought to be exposed to nerve agents from the Khamisiyah munitions demolition, but the model developed and used to estimate veterans who were potentially exposed had critical flaws (GAO, 2004). Vital status was obtained using the VA Beneficiary Identification and Records Locator Subsystem database or Social Security Administration Death Master File for veterans not found in the VA database. Brain cancer deaths were identified using ICD-9-CM codes for cause of death. Medical records were requested and reviewed for persons who died of brain cancer. Cox proportional hazard models were used to calculate RR estimates between deployed and nondeployed veterans.

An alternative method to using mortality data to study the incidence of brain cancer among deployed and nondeployed Gulf War veterans is through the use of linked cancer registry data. Young et al. (2010) linked data from the same cohort of 621,902 deployed veterans and 746,248 era veterans as used in the mortality studies with central cancer registries of 28 states (capturing 84% of the US population) and the VA Central Cancer Registry. Using logistic regression models, proportional incidence ratios were calculated and adjusted for demographic and military characteristics. That approach allows for a relatively complete ascertainment of incident cancers that are diagnosed both within and outside of VA. However, proportional incidence ratios are not ideal for comparing proportional incidence of less frequent outcomes (such as brain cancer) with more frequent outcomes.

Comments on the Use of Algorithms

The committee considered the algorithms discussed above as it considered the ways in which it might be able to design an epidemiologic study as described in the legislation. The algorithms used administrative data from VA and other data sources and demonstrated that there are methods and techniques that can be used to more accurately identify true cases of MS, migraine, Parkinson's disease, and brain cancer. For example, accurately identifying disease onset or incidence without extensive records review or interviewing subjects is difficult for MS and Parkinson's disease. The initial symptoms are often misdiagnosed or vague (coded only as symptoms) with a typical delay in diagnosis of 3 to 5 years before an ICD-9 code for MS or Parkinson's disease is recorded (it might be even longer for progressive non-relapsing MS). No validated algorithms based on administrative data alone exist to identify incident MS cases with a sufficient degree of sensitivity and specificity that would be required to determine whether deployment is associated with the risk of MS. Although the approach used by Wallin et al. (2012) is practical, it might miss cases with a longer than 7-year delay in symptom onset because it relies on service connection status to identify cases, thus likely underestimating the true proportion of progressive MS cases.

Because malignant brain cancers are fatal and usually occur within a relatively short timeframe, death records combined with VA administrative data can accurately identify malignant brain cancers and be used to estimate both incidence and prevalence. In contrast, mortality data are not a good proxy for estimating MS, Parkinson's disease, or migraine incidence or prevalence as these illnesses are chronic and usually not the primary cause of death.

Establishing the prevalence and incidence of people with migraines presents different challenges, necessitating different study designs than for MS, Parkinson's disease, and brain cancer, because people with migraines often do not seek medical attention and are often relieved by over-the-counter or non-pharmacologic treatments. Migraines are often mistaken for other types of headaches both by patients and physicians, and the diagnosis is based entirely on symptoms. Thus, administrative claims data-based algorithms grossly underestimate the prevalence of migraines, serving as a proxy for migraine severity rather than migraine prevalence or incidence.

LIMITATIONS OF USING VA DATA SOURCES

The committee limited its evaluation to existing VA data sources because these would be the only data sources available to the committee. The VA maintains hundreds of databases that collect and store information related to health and other services for veterans. Those databases include, for example, information on inpatient and outpatient procedures, diagnoses, pharmacy data, and service-connected benefits. The VA also conducts surveys of its veterans, for example, the NHS and the National Health Study for a New Generation of US Veterans (NewGen). The committee examined the potential data that could be gleaned from those databases and surveys to determine if they might be useful in designing a study as outlined in the legislation. The committee also reviewed published papers that highlighted the challenges of using those data to determine prevalence, incidence, and risk factors (as required by the legislation). The committee identified three major limitations: (1) constructing a suitable comparison group, (2) using electronic clinical data, and (3) using VA survey data.

Constructing a Suitable Comparison Group

A suitable comparison group is essential for assessing whether deployment is associated with or has a causal effect on the incidence of the conditions of interest. The comparison group in an epidemiologic study should resemble, as closely as possible, the characteristics of the study group so that differences in outcomes can be attributed to the factor of interest (here, deployment) rather than other confounding factors.

Several possible comparison groups were discussed by the committee, including service members who remained stateside during the period of conflict; those who did not deploy to the Afghanistan or Iraq operational theaters, but were deployed elsewhere such as South Korea or Germany; and service members who deployed to Southwest Asia, such as Bahrain, Kuwait, or Qatar, after the 1990-1991 Gulf War ended and before the OEF and OIF conflicts began. Most deployment information (such as locations, number of deployments, length of deployments) is not available from the VA data alone. VA assembled a cohort of 621,902 deployed Gulf War veterans and a random sample of 746,248 era veterans that could be used and would allow for an adequately powered study to determine whether deployment is associated with an increased risk of developing any of the four neurologic conditions of interest.

However, it is not easy to select a comparison group for OEF/OIF/OND active-duty service members because as of December 2011, a majority of members[8] in each service branch deployed at least once to Iraq or Afghanistan (RAND, 2013). Moreover, in contrast to the Gulf War operations, which lasted under 1 year and most service members had a single deployment, as of 2010, 47% of all OEF/OIF/OND active-duty service members, 35% of reservists, and 35% of National Guardsmen deployed more than once and their cumulative lengths of deployment averaged between 15.2 and 17.6 months depending on branch of service and component (IOM, 2013). Those who have not deployed likely differ from the deployed in important characteristics, some of which might be related to the health outcomes of interest. Many of those service members who had not deployed to Iraq or Afghanistan were new recruits in training, had been stationed elsewhere (such as Europe, Japan, or South Korea), or were supporting the operations from posts in the United States. A more representative comparison group might consist of service members who are eligible to deploy but did not. However, only 4% (20,000) of active-duty soldiers met this requirement as of December 2011 (RAND, 2013), and therefore, the statistical power for making comparisons using that group would be limited.

The 1990-1991 Gulf War and OEF/OIF/OND veterans are not comparable to each other, in part, because the demographic makeup of the US military has continued to change between conflicts. For example, 1990-1991 Gulf War deployed service members were 7% female, 70% white/non-Hispanic, 17% reservists or members of the National Guard, and had a mean age of 28 years (IOM, 2010). As of 2010, OEF and OIF service members were 12% female, 77% white/non-Hispanic, 33% reservists or members of the National Guard, and had a mean age of 33.4 years (IOM, 2013). There are methods to adjust for differences in demographic factors to make the Gulf War and OEF/OIF/OND deployed veteran populations more comparable, but inherent differences in conditions and characteristics of deployment and potential exposures experienced in each conflict (for example, multiple chemical exposures in the 1990-1991 Gulf War and the large number of head injuries, concussions, and traumatic brain injury in the OEF/OIF/OND conflicts) limit the adjustments that can be made.

[8] The language of this sentence has been updated since the original release of the report.

An additional consideration in constructing a comparison group for Gulf War and OEF/OIF/OND veterans is the exclusion of veterans who are not using VA services, which might lead to missed cases. Approximately 46% of deployed and 36% of nondeployed Gulf War veterans and 60% of OEF/OIF/OND veterans use VA services (VA, 2014a,b, 2015). In the past, veterans who used VA health care services were, in general, older, had lower income, and had more health problems than nonusers. Therefore, users and nonusers of VA health care might differ in important characteristics that might compromise comparisons between them. That is a major methodologic limitation of studies that seek to compare the effect of deployment based solely on users of VA services.

Even when VA and other data sources are used, constructing a representative study cohort is difficult. Washington et al. (2010) used administrative databases from the DOD, the Veterans Benefits Administration (VBA), and the Veterans Health Administration (VHA) to attempt to create a representative sampling frame for population-based studies of women veterans who served in the Gulf War or OEF and OIF, which would include both users and nonusers of VA services. The authors combined the VHA National Enrollment Database (which is a compilation of data from local VA facilities on all veterans who applied for enrollment for VA health care); the VHA National Patient Care Database (a centralized data warehouse that receives clinical encounter data from VHA clinical information systems); the VBA Compensation and Pension Mini File and Veterans Service Network (which represent data repositories of enrollees for any veteran benefit, including health care); and the DOD Defense Enrollment Eligibility Reporting System (through DMDC), which is a database of active-duty and retired service members and others entitled to receive TRICARE health benefits and includes records for all veterans who separated from the military after 1982. Official estimates and projections of the veteran population were made using the 2007 Veteran Population Projection Model, which incorporates actual numbers of military separations and deaths, and those estimates were used as the denominator for database representativeness estimates. The DOD database identified 100% of OEF and OIF women veterans, whereas the VHA National Enrollment Database identified only 23.5% and the VBA databases identified 13.7% of that group. Although combining all of those administrative datasets expanded the representativeness of the population of veterans for inclusion in research, it still captured only 51.4% of the total population of living women veterans (including 43% who were non-VA users).

Previous research indicates that those deployed to the 1990-1991 Gulf War were different from nondeployed individuals with respect to characteristics that are likely to be associated with later health outcomes. Bell et al. (2000) observed that individuals who were deployed to the 1990-1991 Gulf War were more likely to be in better health before deployment than those who were not deployed, with fewer prewar hospitalizations for any cause and a lower frequency of predeployment depression. Although statistical methods exist to adjust for confounders that are associated with the probability of being deployed (i.e., propensity score matching, inverse probability weighting), these methods require baseline information on predeployment health characteristics, information that is not available within the VA system. A matter that further complicates the goal of identifying an appropriate comparison group is that the process of military training and screening preferentially selects for individuals who are relatively healthy compared with persons in the general US population, the so-called Healthy Warrior effect (Larson et al., 2008). That effect is a consideration only when comparing effect estimates in military or veteran populations with the general US population. With regard to the OEF/OIF/OND population, finding a suitable comparison group might present additional

methodologic challenges that cannot be overcome with statistical methods to adjust for confounding.

Limitations of Using Electronic Clinical Data

Clinical data were not available in electronic health records prior to 1999 (Robert Bossarte, VA, personal communication, March 2015), which particularly affects health information on 1990-1991 Gulf War veterans. Although not unique to the VA data systems, preclinical or prodromal cases are not captured, and time of onset is unknown. However, that information would be necessary to determine the incidence of the diseases of interest.

Additionally, to accurately determine whether deployment is associated with an increased risk of developing MS, migraines, Parkinson's disease, or brain cancer, detailed information and objective measures of possible exposures experienced during deployment, the frequency of each exposure, and the length and route of exposure are needed. However, the only available information on potential exposures is based on self-report measures and surveys that are not included as items in the VA medical records. Likewise, individual-level exposures are not captured in the medical record for OEF/OIF/OND veterans. Finally, the medical records or other administrative databases do not capture potential confounders, such as smoking.

VA maintains hundreds of databases that collect and store different and overlapping information. Its administrative databases were designed for specific purposes and not necessarily for health services research. Researchers did not provide input regarding the design or types of information to be collected, limiting their utility to address research questions (Cowper et al., 1999; Washington et al., 2010). As discussed above, incompleteness of the data, unrepresentativeness of the target population, and coding errors are some of the limitations of using VA administrative data.

Limitations of Using Currently Available Survey Data

VA has conducted three waves of the NHS and a modified baseline health survey in OEF and OIF veterans (NewGen) with response rates that ranged from 34% to 70% (see Appendix B). How and whether the questions included were validated is unknown but all responses are based on self-report. Waves 1 and 2 of the NHS did not have any questions related to MS, Parkinson's disease, or brain cancer (VA, 1995, 2005). The wave 3 survey included separate questions as to whether a respondent had ever been told by his/her doctor that he/she had MS, Parkinson's disease, or brain cancer. If the person answered yes to any of the conditions, the next question asked whether the condition had "been present in the past 4 weeks" (VA, 2012). None of the published papers on those surveys include results on brain cancer.

The NewGen survey did not include any questions on Parkinson's disease, but did include separate questions regarding whether a respondent had ever been told by a doctor that he/she had MS or any cancer (except skin cancer). If the respondent answered yes, he/she was to indicate the year of first diagnosis. Space was provided for respondents to indicate the type of cancer (VA, 2009). The limited information collected by the surveys and unconfirmed responses for MS, Parkinson's disease, and brain cancer questions limit the usefulness of those surveys for use in an epidemiologic study to determine the incidence or the prevalence of the conditions named in the legislation.

All three NHS waves included general questions on headaches and waves 1 and 3 included specific questions on migraines. Wave 1 contained one question on recurrent headaches

and a separate question on migraines during the past 12 months. Persons who indicated a positive response to the condition were then asked to indicate when the problem first occurred (before August 1, 1990; during the time of the conflict, August 1, 1990–June 30, 1991; or after July 1, 1991). If the respondent indicated either during or after the Gulf War conflict, he/she was asked to write in the month and year of onset. No questions about head trauma or other injuries were included (VA, 1995). Two questions on headaches were included in the wave 2 survey; the first asked whether the person had "persistent or recurring problems with" any headaches in the past 12 months. If yes, the person was to indicate whether the headaches were mild or severe (defined at the beginning of the survey section) and whether they had been present for 6 months or longer. The second question asked respondents to indicate how much they had been bothered by headaches in the past 4 weeks (not bothered, bothered a little, or bothered a lot) (VA, 2005). The wave 3 survey asked whether a respondent had ever been told by their doctor that he/she had migraine headaches. If the person answered yes, the next question was whether it had been present in the past 4 weeks. Further in the survey, the same two headache questions that were asked in wave 2 were repeated (VA, 2012).

The NewGen survey asked whether a respondent had ever been told by his/her doctor that he/she had migraines, and if yes, to indicate the year he/she was first diagnosed (VA, 2009). Although more information was collected on headaches and migraines than the other conditions of interest, the questions included in the survey were not from validated screens and the information was not validated using medical records or clinical exams. Questions elucidating potential confounders and risk factors such as experiencing head injury or traumatic brain injury were only included in NewGen. Potentially, information on diagnoses of migraines could be adjusted for being in a blast or explosion, motor vehicle or other crashes, or other head trauma experiences to gain a better understanding of the occurrence of migraines in this population; however, responses to these questions have not been published.

McNeil et al. (2013) conducted a study that evaluated surveys and the research tools used in 12 large epidemiologic studies and 2 registries of Gulf War veterans, including the VA's NHS, and found that many of the instruments used similar questions for certain domains, but that considerable variation existed among survey instruments for questions of health status, psychological status, psychological trauma, and specific diagnoses of fatigue and multisymptom illness.

The committee identified numerous limitations regarding the survey data, such as the failure to use validated screening tools for neurologic conditions, the lack of validation with medical records or clinical exams, the lack of information on confounders or risk factors (with the exception of NewGen), and the low response rates that could result in selection bias. Additionally, the sample size of the surveys is too small to provide adequate power to assess the outcomes of interest with the exception of migraines. The committee does not wish to suggest that an epidemiologic study of migraine is not feasible, rather given the constraint of using only existing VA data would limit case ascertainment to those individuals seeking care, and that the survey data that had been collected on migraine and headache in a selected sample of Gulf War and OEF/OIF/OND veterans was not useful. Given the limitations of the information collected by and comparisons that can be made between multiple surveys, coupled with the absence of specific questions on the neurologic outcomes of interest, the committee perceived the VA surveys as having limited utility in designing an epidemiologic study for its charge.

SUMMARY

The committee members reviewed the scientific literature on the outcomes of concern to better understand the burden of the illnesses in the deployed compared with the nondeployed Gulf War and OEF/OIF/OND populations, to understand how such studies were conducted, and to note their strengths and limitations. The committee considered each outcome separately, to fully understand whether it could design a study for each of the outcomes under consideration. The committee examined possible data sources and data elements that would be needed (in each case, limited to VA data), considered possible study designs and appropriate algorithms to use for case ascertainment, and discussed the challenges of conducting such a study. Ultimately, the committee decided not to proceed with a study that is limited to using existing VA data. However, if additional data (for example, from CDC, CMS, DOD, and others) were made available, then perhaps a more rigorous study could be conducted. The committee is aware of the logistic difficulties of merging data from multiple data sources and across multiple government agencies, the difficulties that persist with regard to access to datasets with identifiable information, and the time and expense that would be required to complete the necessary data use agreements, data linkages, and analyses.

Given all the considerations noted, the committee did, however, consider alternative study designs for each of the neurologic outcomes and considered them separately, because each of them present different study design challenges. Identifying true cases of MS, migraines, Parkinson's disease, or brain cancer with a high degree of precision requires different approaches due to inherent differences in the nature and frequency of those illnesses. In addition, methods that accurately identify true cases suitable for estimating prevalence may not be adequate for identifying disease onset required to define incident cases, with the exception of malignant brain cancer.

Low Burden

The committee reviewed several studies on the outcomes of concern. These studies used both VA and other data sources (primarily DOD data). Studies of 1990-1991 Gulf War deployed veterans observed significantly lower incidence of service-connected MS (Wallin et al., 2012, 2014) and significantly lower MS mortality (Barth et al., 2009) than nondeployed veterans from the same era. The committee examined the VA clinical utilization data for 2001-2013 and also found that the odds of having one or more primary diagnostic codes for MS was statistically significantly lower for Gulf War deployed compared with nondeployed veterans (OR = 0.90, 95% CI: 0.82-0.98). Specifically, of the deployed and nondeployed Gulf War veterans using VA health care services, a primary diagnostic code of MS was listed for 1,040 deployed and 1,089 nondeployed veterans (VA, 2014a,b). With regard to the OEF/OIF/OND VA health care users, 1,529 had a primary diagnosis of MS over the 13-year period (VA, 2015).

Similarly, studies of Parkinson's disease and brain cancer show lower prevalence in deployed veterans when compared with nondeployed veterans. Of those deployed and nondeployed Gulf War veterans using VA health care services, a primary diagnostic code of Parkinson's disease was listed for 403 deployed and 487 nondeployed veterans. The odds of having a primary diagnosis of Parkinson's disease were statistically significantly lower for Gulf War deployed veterans compared with nondeployed veterans (OR = 0.78, 95% CI: 0.68-0.89)

(VA, 2014a,b). VA utilization data for deployed veterans of OEF/OIF/OND using VA health care noted that 332 had a primary diagnosis of Parkinson's disease over the 13-year period.

VA utilization data noted 342 malignant brain cancers in Gulf War deployed veterans and 332 in nondeployed veterans among those using VA health care. The odds of having a primary diagnosis of malignant brain cancer were not statistically different for deployed compared with nondeployed Gulf War veterans (OR = 0.97, 95% CI: 0.83-1.13). Other studies in Gulf War veterans (Barth et al., 2009; Young et al., 2010; Zullig et al., 2012) are consistent in not showing an additional overall risk of brain cancer. With regard to OEF/OIF/OND deployed veterans, VA utilization reports documented 458 malignant neoplasms of the brain out of the 1,126,173 veterans who used VA health care. The committee noted a dearth of studies of Parkinson's disease in the Gulf War and OEF/OIF/OND cohorts likely because they are too young to have developed it.

VA utilization data reported a primary diagnostic code of migraine for 16,327 deployed and 14,115 nondeployed Gulf War veterans. The odds of having a primary diagnosis of migraine were statistically significantly higher for deployed veterans compared with nondeployed veterans (OR = 1.09, 95% CI: 1.07-1.12) (VA, 2014a,b). For OEF/OIF/OND veterans using VA health care, 58,045 had a primary diagnosis of migraine. Several of the studies reviewed found that Gulf War deployed veterans report more headaches and migraines than nondeployed Gulf War veterans (Kang et al., 2000). OEF/OIF/OND combat deployed have increased headaches and migraines compared with noncombat deployed (Jankosky et al., 2011; Theeler et al., 2012).

Difficulty in Constructing a Comparison Group for OEF/OIF/OND

A well-designed epidemiologic study of the neurologic outcomes would require an adequate population size that would allow for a suitable comparison group to be constructed, be representative of all deployed and era veterans for Gulf War and OEF/OIF/OND, and use case ascertainment methods that are sensitive and specific. Investigators designing a study using the OEF/OIF/OND population would have great difficulty identifying an appropriate nondeployed comparison group because as of December 2011 almost all members in each service branch had deployed at least once to Iraq or Afghanistan (RAND, 2013). Many of those service members who had not deployed to Iraq or Afghanistan were new recruits in training, had been stationed elsewhere (such as Europe, Japan, or South Korea), or were supporting the operations from posts in the United States. While the committee could attempt to construct a nondeployed, deployed elsewhere, or eligible to deploy group of veterans, the characteristics of such a group would likely be different from those that deployed to OIF/OEF/OND, thereby limiting the validity of the associations that could be made. Those who have not deployed likely differ from the deployed in important characteristics, some of which might be related to the health outcomes of interest. A more representative comparison group might consist of service members who are eligible to deploy but had not. Only 4% (20,000) of active-duty soldiers who were eligible to deploy had not as of December 2011 (RAND, 2013), and therefore, using that group would limit the statistical power for making comparisons.

Moreover, in contrast to the Gulf War operations, which lasted under 1 year and most service members had a single deployment, as of 2010, 47% of all OEF/OIF/OND active-duty service members, 35% of reservists, and 35% of National Guardsmen deployed more than once and their cumulative lengths of deployment averaged between 15.2 and 17.6 months depending on branch of service and component (IOM, 2013). Those who have not deployed likely differ

from the deployed in important characteristics, some of which might be related to the health outcomes of interest.

Case Ascertainment Using VA Medical Records

Identifying cases for MS or Parkinson's disease is often difficult because no definitive diagnostic tests exist; instead diagnosis is made on clinical grounds and ruling out other conditions. For each medical encounter (inpatient or outpatient), a diagnosis is entered into medical records using ICD-9-CM codes. However, for the conditions of interest, several studies have shown that using a single instance of an ICD-9-CM code in a medical record does not accurately identify the number of true cases, engendering a large number of false positives. Limitations of using ICD-9-CM codes alone to identify cases include coding errors (such as clerical errors, misuse, or omissions), inaccurate diagnoses, and assigning codes prematurely or for uncertain diagnoses. Accurately identifying disease onset or incidence without extensive records review or interviewing subjects is difficult for MS and Parkinson's disease. The initial symptoms are often misdiagnosed or vague (coded only as symptoms) with a typical delay in diagnosis of 3 to 5 years before an ICD-9 code for MS or Parkinson's disease is recorded. Although the approach used by Wallin et al. (2012) is practical, it will likely miss cases with a longer than 7-year delay in symptom onset because it relies on service connection status to identify cases. Thus, for outcomes like MS and Parkinson's disease, there would likely be over ascertainment of cases using ICD codes alone from VA records.

Disease-Specific Challenges

The committee considered alternative study designs for each of the neurologic outcomes separately, because each of them presents different study design challenges. A study to determine the prevalence and incidence of migraines, for example, presents challenges because people with migraines often do not seek medical attention, as they are often relieved by over-the-counter or non-pharmacologic treatments and are often mistaken for other types of headaches both by patients and physicians. The only cases that would be seen in the medical record are those cases that rise to frequent and severe. Thus, at best, a study could be used as a proxy for migraine severity or frequency rather than migraine prevalence or incidence. Additionally, a study would have to account for PTSD and head injury in OEF/OIF/OND veterans.

The committee concluded that not enough time has elapsed to enable an adequately powered study to assess the incidence of Parkinson's disease among Gulf War and OEF/OIF/OND veterans because the age distribution of these group are too young to observe sufficient numbers of Parkinson's disease cases for study. Because the average age of the Gulf War veterans is less than 55, and the average age of OEF/OIF/OND is even younger, Parkinson's disease is not likely to develop for several more years (as the average age of onset is in the sixth to seventh decade). Thus, it is premature to begin a study examining Parkinson's disease. After sufficient time elapses, a study similar to the studies of Wallin et al. (2012, 2014) could be carried out by VA investigators.

CONCLUDING COMMENTS

The committee concluded that while technically feasible, it would not continue with the next steps of designing and implementing a study of the neurologic diseases of concern. In addition to the issues of low burden, the difficulty in constructing a comparison group for the OEF/OIF/OND population, case ascertainment relying solely on VA administrative data, and disease-specific challenges, the primary reason for the committee's conclusion is the restriction to the use of existing VA data, the limitations of which have been well-described in this report. Furthermore, VA and numerous other researchers have already published results on the outcomes of concern using VA data linked to other data sources (e.g., CDC mortality data, DOD), and therefore, it is unlikely that the committee would find different results from those well-designed studies that already have been published and scrutinized (e.g., brain cancer studies by Barth et al. [2009] and Young et al. [2010], and multiple sclerosis by Wallin et al. [2012, 2014]). Given that the committee would be limited to using existing VA data only, an IOM study would essentially repeat the work of Wallin et al. and others yet have the additional limitation of not having access to other important data sources. Thus, the committee did not believe it could advance the knowledge significantly beyond what is already known.

A

INFORMATION REGARDING THE LEGISLATION DIRECTING THE STUDY

S.3023 VETERANS' BENEFITS IMPROVEMENT ACT OF 2008

Section 804. National Academies study on risk of developing multiple sclerosis as a result of certain service in the Persian Gulf War and Post 9/11 Global Operations

(a) IN GENERAL.—The Secretary of Veterans Affairs shall enter into a contract with the Institute of Medicine of the National Academies to conduct a comprehensive epidemiological study for purposes of identifying any increased risk of developing multiple sclerosis as a result of service in the Armed Forces during the Persian Gulf War in the Southwest Asia theater of operations or in the Post 9/11 Global Operations theaters.

(b) ELEMENTS.—In conducting the study required under subsection (a), the Institute of Medicine shall do the following:

(1) Determine whether service in the Armed Forces during the Persian Gulf War in the Southwest Asia theater of operations, or in the Post 9/11 Global Operations theaters, increased the risk of developing multiple sclerosis.

(2) Identify the incidence and prevalence of diagnosed neurological diseases, including multiple sclerosis, Parkinson's disease, and brain cancers, as well as central nervous system abnormalities that are difficult to precisely diagnose, in each group as follows:

(A) Members of the Armed Forces who served during the Persian Gulf War in the Southwest Asia theater of operations.

(B) Members of the Armed Forces who served in the Post 9/11 Global Operations theaters.

(C) A non-deployed comparison group for those who served in the Persian Gulf War in the Southwest Asia theater of operations and the Post 9/11 Global Operations theaters.

(3) Compare the incidence and prevalence of the named diagnosed neurological diseases and undiagnosed central nervous system abnormalities among veterans who served during the Persian Gulf War in the Southwest Asia theater of operations, or in the Post 9/11 Global Operations theaters, in various locations during such periods, as determined by the Institute of Medicine.

(4) Collect information on risk factors, such as pesticide and other toxic exposures, to which veterans were exposed while serving during the Persian Gulf War in the Southwest Asia theater of operations or the Post 9/11 Global Operations theaters, or thereafter.

B

VA AND DOD REPORTS

This appendix describes reports by the Department of Veterans Affairs (VA) and the Department of Defense (DOD). These include the VA utilization reports and surveys conducted by the VA's Office of Public Health and the DOD Medical Surveillance Monthly Report (MSMR).

DEPARTMENT OF VETERANS AFFAIRS UTILIZATION REPORTS

VA releases utilization reports that are updated quarterly. The reports are created by linking the DOD's Defense Manpower Data Center (DMDC) deployment roster files of returning OEF/OIF/OND[8] veterans to the VA's administrative inpatient and outpatient record files. The DOD deployment roster file contains a complete list of separated veterans who have left the theater of operations through November 2014 (for the latest report); the file does not contain a code to distinguish between OEF, OIF, or OND veterans (VA, 2015). Results are presented as cumulative totals that display the number of unique veterans with primary diagnoses or diagnoses in any position by the *International Classification of Diseases Ninth Revision, Clinical Modification* (ICD-9-CM) codes that are obtained from veterans' medical records, from care received at a VA facility (excluding care receive at a Vet Center). Patient records are not reviewed and diagnoses are not confirmed for utilization reports. A veteran can have multiple diagnoses with each health care encounter, and therefore, may be counted in multiple categories, but the person is counted only once in any single diagnostic category. The utilization reports represent only those OEF/OIF/OND veterans using VA health care (approximately 60% or 1,158,359 veterans) since October 1, 2001. Thus, the data in the reports do not represent all 1,906,754 OEF/OIF/OND veterans who have become eligible for VA health care or the approximately 2.7 million service members (as of December 31, 2014) who have served or are currently serving in the Afghanistan and Iraq theaters of operations (VA, 2015).

Similarly, the VA utilization reports for 1990-1991 Gulf War veterans provided health care data gathered between October 1, 2001, and September 30, 2013, and found that 286,995 veterans (46%) of the 621,901 veterans who deployed used VA health care at least once (VA, 2014a). Over that same time period, 269,635 nondeployed Gulf War veterans (36%) used VA health care services at least once out of a total of 746,247 nondeployed (VA, 2014b).

[8]Operation Enduring Freedom (OEF) is the name for the conflict in Afghanistan (October 7, 2001–December 28, 2014). Operation Iraqi Freedom (OIF) is the name of the conflict in Iraq (March 19, 2003–August 31, 2010). On September 1, 2010, Operation New Dawn (OND) became the new name of OIF, which officially ended December 15, 2011.

DEPARTMENT OF VETERANS AFFAIRS SURVEYS

The National Health Survey of Gulf War Era Veterans and Their Families

VA conducted three waves of a longitudinal survey of 1990-1991 Gulf War veterans. There are 30,000 Gulf War veterans (15,000 deployed and 15,000 era[9] veterans) included in the survey known as the National Health Survey of Gulf War Era Veterans and Their Families (NHS). Additionally, there is another similarly designed survey that focuses on the health outcomes of OEF/OIF veterans (National Health Study for a New Generation of US Veterans, or "NewGen"). The first wave of the NHS was conducted in 1993-1995 (Kang et al., 2000) and with physical examinations in 1999-2001 (Eisen et al., 2005). The second wave was conducted in 2003-2005 (Kang et al., 2009), and the third wave was conducted in 2012-2013 (Bossarte, 2015). The NHS was mandated by Public Law 103-446 to be a major population-based study of US veterans and to estimate the prevalence of symptoms and other health outcomes in Gulf War deployed versus era veterans. VA presented results from the three NHS survey waves at the committee's first meeting (Bossarte, 2015), some of which have been published (Kang et al., 2000, 2009; Li et al., 2011).

The study population was selected using a stratified random sample of 15,000 deployed and 15,000 Gulf War era veterans identified by the DMDC and selected from the larger population of approximately 694,000 Gulf War deployed and 800,000 Gulf War era veterans (Kang et al., 2000). Women, National Guard, and reserve service members were oversampled, resulting in a study population that was approximately 20% women, 25% National Guard, and 33% reserves. Each survey wave was administered by mail or computer-assisted telephone interviewing software to those persons who did not respond to the mailed survey. The same cohort of 30,000 was contacted for each survey (Kang et al., 2009). A random sample of respondents (range 1,000-4,200 depending on the wave) were asked to consent to a medical record review that focused on clinic visits and hospitalizations to verify selected self-reported outcomes in the survey. Kang et al. (2000) reported that there was strong correlation between self-reported symptoms, conditions, and reasons for hospitalizations and clinic visits; however, no numbers or statistics were presented.

The baseline 16-page structured health questionnaire included a 48-question symptom inventory (somatic and psychologic symptoms, including severity and time of onset), items on potential environmental risk factors, confounders such as smoking and alcohol use, measures of functional impairment, and medical history (VA, 1995). The overall response rate was 70%; a total of 11,441 (75%) deployed and 9,476 (64%) Gulf War era veterans participated in the study; 15,817 veterans responded to the questionnaire and 5,100 responded to the telephone interview (Kang et al., 2000).

Wave 2 of the NHS, the first follow-up study, took place 10 years after the baseline, it had a 34% response rate (40% deployed veterans and 27% era veterans). The wave 2 survey questionnaire was modified from the baseline version and again collected information about the presence of various symptoms, functional status, health perceptions, chronic medical conditions (self-report of provider diagnoses), mental health disorders, health care utilization, and potential confounders such as the use of alcohol and cigarettes. No questions on environmental exposures

[9]Era veterans typically are defined as nondeployed veterans or veterans deployed elsewhere during the study period.

were included. The questionnaire contained questions from validated self-report assessments, including the Patient Health Questionnaire modules for depression, somatic symptoms, anxiety, and alcohol abuse that could be applied to diagnostic algorithms (Kang et al., 2009; VA, 2005).

Wave 3 of the NHS was conducted in 2015 and had a response rate of 50% (57% deployed, 43% era veterans). Results have not been published, but VA presented an overview of methods and preliminary findings to the committee (Bossarte, 2015). The wave 3 questionnaire was modified from the earlier versions and again collected information about the presence of various symptoms such as headaches and memory problems; functional status; activity limitations; health perceptions; chronic medical conditions (self-report of provider diagnoses); mental health disorders; health care utilization; medications; and potential confounders such as the use of alcohol and cigarettes. No questions on environmental exposures were included (VA, 2012).

National Health Study for a New Generation of US Veterans (NewGen)

NewGen was designed to follow and periodically survey a population of randomly selected OEF and OIF veterans (30,000 deployed and 30,000 era veterans) for 10 years. To be eligible for the study, veterans had to either have been deployed between October 2001 and June 2008 or have served in the military during this period but not deployed. Women were oversampled to comprise 20% of the study population. Using a tiered design, respondents could complete the survey online, use a paper-based form, or by computer-assisted telephone interviewing software for persons who did not respond to the mailed survey, resulting in a 34.4% response rate (49% online; 45% paper; 6% computer-assisted telephone interview) (Eber et al., 2013). Nearly 30% of the selected population could not be located.

The baseline 72-item survey was administered 2009-2011 and included questions on general deployment information, health status, doctor-diagnosed conditions, risk behaviors, use of health care services, potential environmental exposures, smoking and alcohol use, mental health disorders, and experience of trauma and head injuries (VA, 2009).

DEPARTMENT OF DEFENSE

Medical Surveillance Monthly Report

The Armed Forces Health Surveillance Center (AFHSC) issues a monthly report and an annual summary (both since 1995) of morbidity outcomes attributable to various illnesses and injuries. The surveillance population consists of all individuals who served on active duty within any branch from January 1 through December 31 of a given year. The MSMR provides evidence-based estimates of the incidence, distribution, impact, and trends of illness and injuries among US military members and associated populations. Most reports in the MSMR are based on summaries of medical administrative data that are routinely provided to the AFHSC and integrated into the Defense Medical Surveillance System for health surveillance purposes. All medical encounters (both inpatient and outpatient) are included and primary diagnosis is used to summarize ICD-9-CM categories of conditions. In 2014, there were more than 72,500 hospitalizations and 19.4 million ambulatory visits.

C

SUMMARY TABLE

This appendix includes a summary table of selected reports and studies that describe the burden of illness in the 1990-1991 Gulf War and OEF/OIF/OND veteran populations.

Summary of Selected Studies on Disease Burden

REPORTS/ STUDY	VA UTILIZATION REPORTS IN 1990-1991 GULF WAR VETERANS (MS, migraine, PD, brain cancer)	VA UTILIZATION REPORTS IN OEF/OIF/OND VETERANS MS, migraine, PD, brain cancer)	SPECIFIC OUTCOME-RELATED STUDIES (MS)	SPECIFIC OUTCOME-RELATED STUDIES (headache and migraine)	SPECIFIC OUTCOME-RELATED STUDIES (headache disorders)	SPECIFIC OUTCOME-RELATED STUDIES (headache)	SPECIFIC OUTCOME-RELATED STUDIES (cancer, including brain cancer)
Authors	Department of Veterans Affairs (VA)	Department of Veterans Affairs (VA)	Wallin et al. (2014)	Kang et al. (2000)	Jankosky et al. (2011)	Theeler et al. (2012)	Young et al. (2010)
Study Description	Utilization reports of pre 9/11 veterans using the VA health system. Report based on ICD-9 codes for MS, migraine, PD, and malignant neoplasms of the brain. Provides counts for each diagnosis. Based on visits between October 1, 2001, and September 30, 2013.	Utilization reports of post 9/11 veterans using the VA health system. Report based on ICD-9 codes for MS, migraine, PD, malignant neoplasms of the brain. Provides counts for each diagnosis. Based on visits between October 1, 2001, and September 30, 2014.	Evaluated the risk of developing MS and other central nervous system demyelinating diseases (ODDs) in 1990-1991 Gulf War veterans. Cases of MS and ODD were matched to a DOD database of all active-duty personnel. All cases evaluated for service connection.	Survey data used to report outcomes related to headaches and migraines in veterans of the 1990-1991Gulf War. Self-reported responses were used to calculate weighted estimates of population rates for the conditions.	Examined headache disorder in a large population-based US military cohort (using the Millennium Cohort)—a 21-year longitudinal study. Began in 2001 prior to OEF and OIF.	Designed to determine prevalence, characteristics, and factors associated with chronic daily headache.	Studied cancer diagnoses in Gulf War era veterans. Using files from the DMDC and linked with 28 state cancer registries and the VA cancer registry.

REPORTS/ STUDY	VA UTILIZATION REPORTS IN 1990-1991 GULF WAR VETERANS (MS, migraine, PD, brain cancer)	VA UTILIZATION REPORTS IN OEF/OIF/OND VETERANS MS, migraine, PD, brain cancer)	SPECIFIC OUTCOME-RELATED STUDIES (MS)	SPECIFIC OUTCOME-RELATED STUDIES (headache and migraine)	SPECIFIC OUTCOME-RELATED STUDIES (headache disorders)	SPECIFIC OUTCOME-RELATED STUDIES (headache)	SPECIFIC OUTCOME-RELATED STUDIES (cancer, including brain cancer)
Number of Subjects	286,995 deployed veterans	1,126,173 OEF/OIF/OND veterans	696,118 deployed Gulf War veterans	15,000 Gulf War veterans	38,361 combat deployed	978 US Army	621,902 deployed and 746,248 era Gulf War veterans
Comparison Group	269,635 nondeployed using VA health care services	None	1,786,215 nondeployed veterans	15,000 era veterans	Non-combat deployed	US population	Gulf War veterans and Gulf War era veterans
Data Collection Methods	Provide counts for selected health care diagnoses for veterans using VA health care.	Provide counts for selected health care diagnoses for veterans using VA health care.	An incident cohort of MS and ODD was assembled from Gulf War era veterans (1990-2007). Cases of MS and ODD were matched to a database of all active-duty personnel from DOD.	Phase 1: 16-page structured questionnaire sent to each of the 30,000 veterans. Phase 2: telephone interviews on the nonrespondents.	Baseline cohort: A random sample of 256,400 service members of the 2.2 million total serving as of October 1, 2000. Approximately 77,000 completed the baseline questionnaire; those with missing outcome data were excluded.	Self-administered questionnaire	Review of DMDC, state cancer registries, and VA cancer registry

REPORTS/ STUDY	VA UTILIZATION REPORTS IN 1990-1991 GULF WAR VETERANS (MS, migraine, PD, brain cancer)	VA UTILIZATION REPORTS IN OEF/OIF/OND VETERANS MS, migraine, PD, brain cancer)	SPECIFIC OUTCOME-RELATED STUDIES (MS)	SPECIFIC OUTCOME-RELATED STUDIES (headache and migraine)	SPECIFIC OUTCOME-RELATED STUDIES (headache disorders)	SPECIFIC OUTCOME-RELATED STUDIES (headache)	SPECIFIC OUTCOME-RELATED STUDIES (cancer, including brain cancer)
Findings	MS (ICD-9 340): deployed 1,040; nondeployed 1,089 Migraine (ICD-9 346): deployed 16,327; nondeployed 14,115 PD (IDC-9 332.0): deployed 403; nondeployed 487 Malignant neoplasm of the brain (ICD-9 191): deployed 342; nondeployed 332	MS (ICD-9 340): 1,529 deployed Migraine (ICD-9 346): 58,045 deployed PD (IDC-9 332.0): 322 deployed Malignant neoplasm of the brain (ICD-9 191): 458 deployed There are no data on the nondeployed	For 1990-1991 Gulf War veterans: MS and ODD: 1,841 incident cases: 387 cases among the 696,118 deployed and 1,454 cases among the 1,786,215 nondeployed RR for MS 0.69 (95% CI: 0.61-0.78)	Migraines: 16.5% of the deployed and 9.3% of the era veterans Recurring headaches 32.6% of deployed and 14.9% of the era veterans	Combat deployed had statistically significantly higher adjusted odds of new-onset headache disorder than nondeployed (OR = 1.72, 95% CI 1.55-1.90 for men and OR = 1.84, 95% CI 1.55-2.18 for women). Those deployed without combat did not have statistically significantly different adjusted odds of new onset headaches compared to the nondeployed (OR = 1.07, 95% CI 0.95-1.21 for men; OR = 0.96, 95% CI 0.80-1.14 for women).	Findings indicate that the prevalence of chronic daily headache is four to five times higher in OEF and OIF than the US population. Chronic daily headache following concussion often resembles chronic migraine and is associated with onset of headaches within the first week after concussion.	Brain cancer: 278 in deployed and 410 in era Gulf War veterans. The PIR, comparing Gulf War deployed and era veterans: 0.86% (95% CI: 0.73-1.01).

REPORTS/ STUDY	VA UTILIZATION REPORTS IN 1990-1991 GULF WAR VETERANS (MS, migraine, PD, brain cancer)	VA UTILIZATION REPORTS IN OEF/OIF/OND VETERANS MS, migraine, PD, brain cancer)	SPECIFIC OUTCOME-RELATED STUDIES (MS)	SPECIFIC OUTCOME-RELATED STUDIES (headache and migraine)	SPECIFIC OUTCOME-RELATED STUDIES (headache disorders)	SPECIFIC OUTCOME-RELATED STUDIES (headache)	SPECIFIC OUTCOME-RELATED STUDIES (cancer, including brain cancer)
Strengths/ Limitations	Limited to those veterans using VA health care services. Captures approximately 46% of deployed, 36% of nondeployed. Based solely on a single entry of an ICD code for the disease of interest.	Limited to those veterans using VA health care services. Captures approximately 60% of deployed. Based solely on a single entry of an ICD code for the disease of interest.	Strengths include prospective study design, use of incident MS cases within the entire 1990-1991 Gulf War active-duty population; adequate power; and follow-up time to detect significant changes in MS risk in deployed troops. Limitations of the study: the possibility of missing some MS cases that may have had their first symptom outside the active-duty period and 7 years thereafter.	A strength is the large number of subjects who were randomly selected. Limitations of this study include exposure and outcomes data are based on the self-reported data that may be subject to recall bias. The differential participation rate between Gulf War veterans and era veterans could contribute to a biased prevalence estimate.	Strengths include the ability to estimate headache prevalence at baseline and new onset headache disorders at follow-up. Limitations include long post-deployment time frame; possible combat exposure misclassification; types of headaches not distinguished; inability to assess the lifetime prevalence of headache disorders at follow-up.	Limitations include retrospective reporting of headaches, recall errors in reporting headache frequency, blast exposures, and symptoms of concussion. Screening for pre-existing headaches was not performed. The study may not be representative of all US service members with a deployment-related concussion as it was conducted at a single US Army installation.	Strengths include associating cancer incidence outcomes with the entire Gulf War veteran population; included a large and representative sample of era veterans. Outcome assessment based on cancer registry data rather than mortality, hospitalization, or self-reports. Limitations include lack of data from all 50 states and use of different registries may have resulted in slightly different match rates.

NOTE: CI = confidence interval; DMDC = Defense Manpower Data Center; DOD = Department of Defense; ICD = *International Classification of Diseases*; MS = multiple sclerosis; ODD = other demyelinating disease; OEF = Operation Enduring Freedom; OIF = Operation Iraqi Freedom; OR = odds ratio; PD = Parkinson's disease; PIR = Proportional Incidence Ratio; RR = relative risk; VA = Department of Veterans Affairs.

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