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Gulf War and Health
Volume 10

Update of Health Effects of Serving in the Gulf War
2016

Committee on Gulf War and Health, Volume 10: Update of Health Effects of Serving in the Gulf War

Board on the Health of Select Populations

Institute of Medicine

Deborah Cory-Slechta and Roberta Wedge, *Editors*

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COMMITTEE ON GULF WAR AND HEALTH, VOLUME 10: UPDATE OF HEALTH EFFECTS OF SERVING IN THE GULF WAR

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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:

Kate Applebaum, George Washington University
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Simon Wessley, King's College, London
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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Harold C. Sox,** The Patient-Centered Outcomes Research Institute, and **Maryellen L. Giger,** The University of Chicago. 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.

PREFACE

The last nine Institute of Medicine committees that prepared the *Gulf War and Health* series of reports have diligently assessed the evidence for possible health effects associated with exposures experienced by veterans during the Gulf War. All the prior committees, as well as the current committee, have sought to identify diseases and health conditions caused by Gulf War exposures to help the Department of Veterans Affairs (VA) care for those veterans who were harmed. Several volumes in this series have recommended carefully designed research endeavors in the hope of finally understanding the long-term health effects caused by the war.

Unfortunately, all of the Gulf War and Health committees have faced similar challenges in their attempts to identify the health effects that are clearly the result of deployment to the Gulf War. Foremost among these is the ever unknowable impact of the various chemical exposures that occurred during the 1990-1991 Gulf War, whether alone or in combination with other environmental, chemical and/or genetic factors. Objective exposure data gathered during and after the war have been, and are expected to continue to be, unavailable.

Studies of Gulf War illness specifically, the most frequently reported health outcome in these veterans, have been hampered by the relatively amorphous nature of the disorder and its multiple definitions over the past two decades, including chronic multisymptom illness, Gulf War syndrome, and multiple unexplained physical symptoms. Even though the evidence base for Gulf War illness has increased over the past few years, it has provided little new information that has increased our understanding of the disease or how to effectively treat or manage it.

The committee's discussions also included the potential significance of both time and aging, both of which can present substantial difficulties for research efforts. Specifically, the time that has elapsed since the war—25 years—brings with it the potential to impact veterans' recall of events, including the frequency, duration, and intensity of their exposures during their service. At the same time, advancing age can provoke new health concerns and the development of new diseases long after the war. In any population, it can be difficult to distinguish aging-related effects from those caused by a war many years ago. The committee emphasized that some health consequences with a long latency period, such as some cancers and neurodegenerative conditions, may not yet be fully described or be characterized by Gulf War illness. While the symptoms of Gulf War illness are expected to have developed soon after the deployment, similar symptoms, such as headache or cognitive problems, appearing 20 years after the war are unlikely to be related to Gulf War service but may be caused by other exposures or conditions that are entirely unrelated to the Gulf War. Thus, it is ever more important that any future research endeavors use well-designed protocols to minimize the effects of time and aging on the interpretation of Gulf War veterans' health.

The committee did take note of research focused on the determination of potential biomarkers for Gulf War illness; this focus highlights the importance of exploring all avenues of research that might prove fruitful in diagnosing and treating veterans with this debilitating illness. Critical to both the diagnosis and treatment of Gulf War illness, however, is

acknowledging the brain–body continuum. This committee concurs with the findings of previous Gulf War and Health committees in that Gulf War illness is not a psychosomatic illness, and it is cognizant of the residual stigma associated with having a mental health disorder and veterans' frustration of being told that their persistent and disabling symptoms are "all in their heads." Nevertheless, as the committee has tried to emphasize, there is a requisite interconnectedness of the physiological systems of the body and the brain, such that dysfunctions of either have consequences that can extend to both. In the same context, the committee has also tried to reiterate that although Gulf War illness should not be called a psychosomatic disorder, this does not mean that it or any chronic disease, including cancer, diabetes, and heart disease, does not have psychological components that might be amenable to mental health therapies as well as other treatments. For example, many investigations into biomarkers of Gulf War illness acknowledge this brain–body continuum by looking for explanations of the illness in brain functioning. The committee believes it would be a disservice to Gulf War veterans to ignore treatments that might address the mental health and neurocognitive components of Gulf War illness.

The committee would like to acknowledge and give sincere thanks to Dr. Ralph Loren Erickson and Dr. Robert Bossarte of VA; Dr. Beatrice Golomb and Dr. Roberta White from the VA Research Advisory Committee on Gulf War Veterans' Illnesses (RAC); Ronald Brown and James Bunker from the National Gulf War Resource Center, Mr. James Binns and Dr. Lea Steele, former RAC members; Remington Nevin; Denise Nichols, Anthony Hardie, Peter Sullivan, Daniel Sullivan, David Hatfield, and the other Gulf War veterans for their presentations to the committee which it found both illuminating and moving. The committee would also like to thank Dr. Carolyn Clancy, Under Secretary for Health of VA, for her informative remarks.

The committee gained valuable insight and context from the many veterans who attended the committee's first and second meetings or participated by phone. Their experiences and concerns emphasized the seriousness of their health conditions even 25 years after the Gulf War. Their needs and concerns resonated with the committee as it endeavored to review the evidence objectively. The committee sincerely thanks the many individual veterans and veteran service organization representatives who took the time and made the effort to inform the committee's deliberations.

I would like to express my sincere gratitude to the expert committee members for their thoughtfulness, insights, and hard work. I know I speak for the entire committee in expressing many thanks to Roberta Wedge for efficiently guiding the report through its various stages and keeping the committee organized and moving forward; to Cary Haver and Anne Styka for their research efforts; to Nicole Freid for her administrative support, and to the National Academies Research Center's Daniel Bearss for creating and executing the literature search strategy and Ellen Kimmel for fact checking.

Deborah Cory-Slechta, *Chair*
Committee on Gulf War and Health, Volume 10: Update of Health Effects
of Serving in the Gulf War

CONTENTS

ACRONYMS

AChE	acetylcholinesterase
ACR	American College of Rheumatology
AFQT	Armed Forces Qualifying Test
ALS	amyotrophic lateral sclerosis
ANCOVA	analysis of covariance
BAI	Beck Anxiety Inventory
BARS	Behavioral Assessment and Research System
BChE	butyrylcholinesterase
BIRLS	Beneficiary Identification Records Locator System
BMI	body mass index
BSI	Brief Symptom Inventory
CAPS	Clinician Administered PTSD Scale
CASS	Composite Autonomic Severity Score
CCD	Canadian Cancer Database
CCEP	Comprehensive Clinical Evaluation Program
CDC	Centers for Disease Control and Prevention
CES	Combat Exposure Scale
CFS	chronic fatigue syndrome
CI	confidence interval
CIDI	Composite International Diagnostic Interview
CMD	Canadian Mortality Database
CMI	chronic multisymptom illness
CMV	cytomegalovirus
CNS	central nervous system
COD	cause of death
COMPASS	Composite Autonomic Symptom Scale
COPD	chronic obstructive pulmonary disease
COSHPD	California Office of Statewide Health Planning and Development
Cr	creatinine
CVLT	California Verbal Learning Test
CWP	chronic widespread pain
DASA	Defence Analytical Services Agency (United Kingdom)
DEET	N,N-diethyl-meta-toluamide
DIS	Diagnostic Interview Schedule
DMDC	Defense Manpower Data Center
DNA	deoxyribonucleic acid
DND	Department of National Defence (Canada)
DoD	Department of Defense
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
DSP	distal symmetric polyneuropathy

DU	depleted uranium
EBV	Epstein-Barr virus
EEG	electroencephalography
FA	fractional anisotrophy
FARS	Fatality Analysis Reporting System
FEV_1	forced expiratory volume in 1 second
FGID	functional gastrointestinal disorder
FSH	follicle stimulating hormone
FUS/TLS	fused in sarcoma/translocated in sarcoma
FVC	forced vital capacity
GAD	generalized anxiety disorder
GAO	Government Accountability Office
GHQ-12	12-item General Health Questionnaire
GI	gastrointestinal
GW	Gulf War
GWV	Gulf War veterans
HFM	hemofacial microsomia
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal axis
HR	hazard ratio
HSC	Health Symptoms Checklist
IBS	irritable bowel syndrome
ICD	*International Statistical Classification of Diseases and Related Health Problems*
IOM	Institute of Medicine
IPGWSG	Iowa Persian Gulf War Study Group
IQ	intelligence quotient
LH	luteinizing hormone
MANOVA	multivariate analysis of variance
MCH	mean corpuscular hemoglobin
MCS	multiple chemical sensitivity
MCV	mean corpuscular volume
MD	mean diffusivity
MDD	major depressive disorder
MRI	magnetic resonance imaging
MRR	mortality rate ratio
MS	multiple sclerosis
MSI	unexplained multisymptom illness

NAA	N-acetyl aspartate
NART	National Adults Reading Test
NAS	National Academy of Sciences
NDI	National Death Index
NDV	nondeployed veterans
NHSCR	National Health Service Central Register
NIFS	Nuclear Industry Family Study
NIH	National Institutes of Health
NIS	Neuropathy Impairment Score
NS	Not significant
ODTP	Oregon Dual Task Procedure
OR	odds ratio
PASAT	Paced Auditory Serial Addition Test
PB	pyridostigmine bromide
PCA	principal components analysis
PCL	patient checklist
PCL-C	Patient Checklist-Civilian
PCL-M	Patient Checklist-Military
PFT	pulmonary function test
PHQ	Patient Health Questionnaire
P.L.	public law
PIR	proportional incidence ratio
PMR	proportional morbidity ratio
PON1	paraoxonase-1
POW	prisoner of war
PR	prevalence ratio
PRIME-MD	Primary Care Evaluation of Mental Disorders
PTSD	posttraumatic stress disorder
QoLI	quality of life index
RAC	VA Research Advisory Committee on Gulf War Veterans' Illnesses
RNA	ribonucleic acid
ROI	region of interest
RoM	ratio of means
RR	relative risk (or risk ratio as indicated in text)
SCAN	Schedule for Clinical Assessment and Diagnosis
SCID	Structured Clinical Interview for *DSM-III-R*
SCL	symptom check list
Sd	standard deviation
SEER	Surveillance Epidemiology and End Results Program
SEID	systemic exertion intolerance disease
SF-12	12-Item Short Form Health Survey

SF-36	36-Item Short Form Health Survey
SIR	standardized incidence ratio
SMR	standardized mortality ratio
SMRR	summary mortality rate ratio
SNAP	Special Needs Assessment Profile or Schedule for Nonadaptive and Adaptive Personality
SRR	standardized rate ratio
SSA	Social Security Administration
SWMT	Sternberg working memory task
TBI	traumatic brain injury
TOMM	Test of Memory Malingering
U.S.	United States
UK	United Kingdom
VA	Department of Veterans Affairs
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
WMS	Wechsler Memory Scale

SUMMARY

In response to the invasion of Kuwait by Iraq in August 1990, the United States led a coalition of 34 countries in a buildup of forces in the Persian Gulf called Operation Desert Shield. This multinational effort was followed by Operation Desert Storm, which began in January 1991 with an air offensive and a 4-day ground war. The war was over by the end of February, and a ceasefire was signed in April 1991. Of the almost 700,000 U.S. troops deployed to the Persian Gulf region during the height of the buildup, only about 50,000 U.S. troops were still in the region by June 1991. Although brief with relatively few injuries and deaths among the coalition forces, the legacy of the war has been a substantial contingent of veterans who suffer from a number of health problems that have persisted for over 25 years.

As in any war, the service members who were deployed to the theater of conflict were exposed to many hazardous agents and situations, both known and unknown. These exposures ranged from chemical and biological agents to mandatory vaccines, as well as oil-well fire smoke, dust, high ambient temperatures and heat stress, pesticides, and pyridostigmine bromide (PB), a prophylactic agent against potential nerve agent exposure.

During and after the Gulf War, veterans began reporting a variety of health problems, particularly a constellation of symptoms that have been termed Gulf War illness, and these problems continue to plague many of them to this day. In 1998, in response to the health concerns of the veterans, Congress passed two laws: P.L. 105-277, the Persian Gulf War Veterans Act, and P.L. 105-368, the Veterans Programs Enhancement Act. Those laws directed the secretary of veterans affairs to enter into a contract with the National Academy of Sciences (NAS) to review and evaluate the scientific and medical literature regarding associations between illness and exposure to toxic agents, environmental or wartime hazards, or preventive medicines or vaccines associated with Gulf War service and directed the secretary to consider the NAS conclusions when making decisions about compensation. NAS assigned the study to the Institute of Medicine (IOM), now part of the National Academies of Sciences, Engineering, and Medicine.

The nine prior reports in the *Gulf War and Health* series deal with specific deployment exposures or veteran health status:

Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines
Volume 2: Insecticides and Solvents
Volume 3: Fuels, Combustion Products, and Propellants
Volume 4: Review of the Scientific Literature

Volume 5: Infectious Disease
Volume 6: Physiologic, Psychologic, and Psychosocial Effects of Deployment-Related Stress
Volume 7: Long-Term Consequences of Traumatic Brain Injury
Volume 8: Update of *Health Effects of Serving in the Gulf War*
Volume 9: Long-term Effects of Blast Exposures

CHARGE TO THE COMMITTEE

The specific charge to the Volume 10 committee, as requested by the Department of Veterans Affairs (VA), is to

> comprehensively review, evaluate, and summarize the available scientific and medical literature regarding health effects in the 1990–1991 Gulf War veterans. The committee will pay particular attention to neurological disorders (e.g., Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, and migraines), cancer (especially brain cancer and lung cancer), and chronic multisymptom illness. The proposed study will update earlier IOM reviews on Gulf War and Health, and this volume (Volume 10) will update the literature since the publication of the 2006 (Volume 4) and 2010 (Volume 8) *Gulf War and Health* reports. The committee will also provide recommendations for future research efforts on Gulf War veterans.

THE COMMITTEE'S APPROACH

The committee held two public sessions to put its efforts in context and to clarify an approach to its task. The committee heard from representatives of VA and from several Gulf War veterans about their health conditions that have persisted since the war, particularly the symptoms associated with Gulf War illness. The committee also heard presentations from representatives of the VA Research Advisory Committee on Gulf War Veterans' Illnesses, who discussed that committee's findings and recommendations, and from several researchers who have been studying Gulf War illness. The committee did not address policy issues, such as service connection, compensation, or the cause of or treatment for Gulf War illness.

Extensive searches of the epidemiologic literature were conducted using the same search strategy as for Volume 8. Literature searches were also conducted to look for studies of Gulf War illness or other toxicologic endpoints using animals, in which the animals were exposed to a mixture of agents that attempted to simulate those experienced by Gulf War veterans during deployment. The committee adopted a policy of using only peer-reviewed publications as the basis of its conclusions except for some government reports and one presentation. Accordingly, committee members read each study critically and considered its relevance and quality. The committee did not collect original data, nor did it perform any secondary data analysis.

To be comprehensive in its approach to the epidemiologic literature, the committee also reviewed the studies that had been included in Volumes 4 and 8 as primary or secondary studies and the conclusions reached by those committees. The Volume 10 committee then considered the epidemiologic studies identified in the updated literature search. Those studies were also

reviewed and classified as primary or secondary, according to the criteria discussed below. The committee considered the entire body of relevant literature and determined the strength of associations between being deployed to the Gulf War and specific health outcomes on the basis of all the primary studies and supported by the secondary studies. Although the majority of the studies considered by the committee for this report were epidemiologic, other types of studies—such as animal toxicology, neuroimaging, and genetics—were assessed in the same manner as other health conditions.

Primary and Secondary Studies

For a study to be included in the committee's review as primary it had to meet specified criteria. It had to be published in a peer-reviewed journal or other rigorously peer-reviewed publication, such as a government report or monograph; have sufficient detail to demonstrate rigorous methods (for example, had a control or reference group, and included adjustments for confounders when needed, included necessary level of detail of the methods); include information regarding a persistent health outcome; and use appropriate laboratory testing, if applicable. Furthermore, the sample size needed to suggest that it was generalizable to and representative of the Gulf War veteran population.

Studies reviewed by the committee that did not necessarily meet all the criteria of a primary study were considered secondary studies. Secondary studies are typically not as methodologically rigorous as primary studies and might present subclinical findings, that is, studies of altered functioning consistent with later development of a diagnosis but without clear predictive value. Many of the secondary studies relied on self-reports of various diagnoses rather than an examination by a health professional or a medical record review.

The Volume 10 committee also included a number of studies that did not meet the criteria for a primary or secondary study, but nonetheless provided information on the health of Gulf War veterans. In an effort to be inclusive, these ancillary studies are discussed in a section called "Other Related Studies" for each health outcome to which they pertain; however, no conclusions were based solely on these ancillary studies.

Categories of Association

The committee attempted to express its judgment of the available data clearly and precisely. It agreed to use the categories of association that have been established and used by previous Gulf War and Health and other IOM committees that have evaluated scientific literature. Those categories of association have gained wide acceptance for more than a decade by Congress, government agencies (particularly VA), researchers, and veterans groups.

The committee members read each of the studies carefully, noted the studies' findings and limitations, and discussed the classification of each study (primary or secondary) in plenary session. The committee then discussed the weight of the evidence and reached consensus on the categorization of association to be assigned for each health outcome considered in this report. The five categories below describe different levels of association and present a common message: the validity of an observed association is likely to vary with the extent to which common sources of spurious associations could be ruled out as the reason for the association. Accordingly, the criteria for each category express a degree of confidence based on the extent to which sources of error were reduced.

Sufficient Evidence of a Causal Relationship

Evidence is sufficient to conclude that a causal relationship exists between being deployed to the Gulf War and a health outcome. The evidence fulfills the criteria for sufficient evidence of a causal association in which chance, bias, and confounding can be ruled out with reasonable confidence. The association is supported by several of the other considerations such as strength of association, dose–response relationship, temporal relationship, and biologic plausibility.

Sufficient Evidence of an Association

Evidence suggests an association, in that a positive association has been observed between deployment to the Gulf War and a health outcome in humans; however, there is some doubt as to the influence of chance, bias, and confounding.

Limited/Suggestive Evidence of an Association

Some evidence of an association between deployment to the Gulf War and a health outcome in humans exists, but this is limited by the presence of substantial doubt regarding chance, bias, and confounding.

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

The available studies are of insufficient quality, validity, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between deployment to the Gulf War and a health outcome in humans.

Limited/Suggestive Evidence of No Association

There are several adequate studies, covering the full range of levels of exposure that humans are known to encounter, that are consistent in not showing an association between exposure to a specific agent and a health outcome at any level of exposure. The possibility of a very small increase in risk at the levels of exposure studied can never be excluded.

MAJOR COHORT STUDIES

As noted in earlier volumes, the largest studies of Gulf War veterans have been conducted in countries that were members of the Gulf War coalition, including the United States, the United Kingdom, Canada, Denmark, and Australia. Most major cohorts, once established, led to numerous studies that examined more detailed questions about Gulf War veterans' health; the committee refers to these as derivative studies. The committee organized the literature into the major cohorts and derivative studies because it did not want to interpret the findings of the same cohorts as though they were results for unique groups. The cohort studies of Gulf War veterans and the derivative studies have contributed greatly to our understanding of veterans' health, but they have some of the limitations that are commonly encountered in epidemiologic studies, such as lack of representativeness, selection bias, lack of control for potential confounding factors, self-reporting of health outcomes, and self-reporting of exposure.

The committee considered studies that used both population-based cohorts and cohorts based on military units. Since Volume 8, few studies have been published on the large veteran cohorts. Several of the new studies reviewed by the Volume 10 committee used data from a large

nationally representative study by VA of Gulf War deployed and nondeployed veterans, and further assessments of the entire Australian military contingent deployed to the Gulf War.

HEALTH OUTCOMES

The Volume 10 committee reviewed new and old studies from the epidemiologic literature on Gulf War veterans and used those studies to form the basis of the committee's conclusions regarding associations between deployment to the Gulf War and long-term health outcomes. Most of the studies compared the prevalence of a given medical condition or symptom in the deployed veterans with the prevalence in nondeployed veterans. A small number of studies also looked at the prevalence of health conditions linked to exposure to depleted uranium. For several outcomes only one study, or in some cases no studies, were of sufficient quality to meet the criteria for a primary study. For health outcomes for which new evidence was available, the data tended to support conclusions that generally were in accordance with the findings of prior Gulf War and Health committees.

ANIMAL STUDIES

The committee reviewed over 50 animal studies that used a variety of protocols to assess multiple chemical and other exposures (e.g., simultaneous or sequential exposure to pyridostigmine bromide [PB], pesticides, and stress) that attempted to simulate Gulf War exposures. However, the wide variation in the exposure models and in the number and types of outcomes that were assessed (for example, effects on brain, behavior, reproductive, musculoskeletal, immune, and pain), make comparisons across the animal studies difficult. Most animal studies tended to focus on isolated symptoms of Gulf War illness, again adding to the uncertainty about how representative the effects seen in animals were of veterans' symptoms. In addition, the observed effects were not usually replicated by other researchers, making it difficult to conclude whether the animal models provide support for linking Gulf War exposures to veterans' health outcomes, particularly with regard to Gulf War illness. Thus, animal studies have not been successful in suggesting a mechanism by which deployment exposures during the Gulf War might lead to Gulf War illness or its many symptoms.

The committee concludes that although the existence of an animal model would be advantageous for identifying and evaluating treatment strategies for Gulf War illness, it cautions that developing such an animal model is not possible given researchers' inability to realistically determine the exposures associated with Gulf War service, let alone the frequency, duration, or dose of those exposures, or the effect of multiple exposures.

FINDINGS AND RECOMMENDATIONS

Between 1994 and 2014, federally funded research on Gulf War veterans has totaled more than $500 million (VA, 2015). This large amount of funding has produced many findings, but there has been little substantial progress in our overall understanding of the health effects resulting from deployment to the 1990–1991 Gulf War, particularly Gulf War illness.

Although the committee focused on the epidemiologic literature in making its findings, it also attempted to look at the literature more broadly to identify any information that might provide a more comprehensive picture of the onset, diagnosis, and presentation of the illnesses affecting Gulf War veterans. For example, the committee considered information that might indicate promising areas of research, such as underlying biologic mechanisms of disease, methods for differential diagnoses, or the presence of comorbidities such as obesity or depression, and their potential interactions.

In spite of a thorough literature search, the Volume 10 committee found little evidence to warrant changes to the conclusions made by the Volume 8 committee regarding the strength of the association between deployment to the Gulf War and adverse health outcomes. For several outcomes, only one, or in some cases no, study was of sufficient quality to meet the criteria for a primary study. For health outcomes for which new evidence was available, it tended to support conclusions that were, for the most part, in accordance with the findings of prior Gulf War and Health committees. Veterans who were deployed to the Gulf War do not appear to have an increased risk for many long-term health conditions with the exceptions of posttraumatic stress disorder (PTSD), Gulf War illness, chronic fatigue syndrome, functional gastrointestinal conditions, generalized anxiety disorder, depression, and substance abuse. Indeed, the constellation of symptoms and symptom clusters referred to as Gulf War illness (e.g., fatigue, muscle and joint pain, and cognitive problems) is the signature adverse health outcome of having served in the Persian Gulf region. Multiple studies found that some Gulf War veterans, regardless of their country of origin and their different deployment-related exposures, have persistent, debilitating, and varying symptoms of Gulf War illness. The committee's assessment of the association between deployment to the Gulf War and specific health conditions are briefly summarized in Box S-1.

In response to its statement of task, the committee paid special attention to Gulf War illness, neurologic conditions, and lung and brain cancer. The committee's findings and recommendations on those health conditions and other aspects of Gulf War veteran health are summarized below.

Gulf War Illness

In spite of over 2 decades of studies to help define, diagnose, and treat the multitude of symptoms that are characteristic of Gulf War illness, little progress has been made in elucidating the pathophysiologic mechanisms that underlie the condition, the exposures that may have caused it, or treatments that are generally effective for veterans who suffer from it. The committee that worked on Volume 4 of the *Gulf War and Health* series first indicated that deployed veterans suffer from more signs and symptoms such as headache, joint and back pain, fatigue and sleep problems, and cognitive dysfunction, than do nondeployed veterans. The increased prevalence of numerous symptoms has been seen in Gulf War veterans from the United States as well as several of the coalition countries (e.g., Australia, United Kingdom, and Denmark).

Gulf War illness is not an easily diagnosed condition. It presents with diverse symptom clusters, many of which overlap with other health conditions such as chronic fatigue syndrome, neurodegenerative disorders, and musculoskeletal problems, and there are multiple definitions of it. Based on available research data, it does not appear that a single mechanism can explain the

BOX S-1
Summary of Conclusions Regarding Associations Between Deployment to the Gulf War and Specific Health Conditions

Sufficient Evidence of a Causal Relationship

- Posttraumatic stress disorder (PTSD)

Sufficient Evidence of an Association

- Generalized anxiety disorder, depression, and substance abuse (particularly alcohol abuse)
- Gastrointestinal symptoms consistent with functional gastrointestinal disorders such as irritable bowel syndrome and functional dyspepsia
- Chronic fatigue syndrome
- Gulf War illness

Limited/Suggestive Evidence of an Association

- Amyotrophic lateral sclerosis (ALS)
- Fibromyalgia and chronic widespread pain
- Self-reported sexual difficulties

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

- Any cancer
- Cardiovascular conditions or conditions of the blood and blood-forming organs
- Endocrine, nutritional, and metabolic conditions
- Neurodegenerative diseases other than ALS and multiple sclerosis
- Neurocognitive and neurobehavioral performance
- Migraines and other headache disorders
- Other neurologic outcomes
- Respiratory diseases
- Structural gastrointestinal diseases
- Chronic skin conditions
- Musculoskeletal system diseases
- Genitourinary conditions
- Specific birth defects
- Adverse pregnancy outcomes such as miscarriage, stillbirth, preterm birth, and low birth weight
- Fertility problems
- Increased mortality from any cancer, any neurologic disease (including multiple sclerosis, Alzheimer's disease, Parkinson's disease, and ALS), respiratory disease, or gastrointestinal disease

Limited/Suggestive Evidence of No Association

- Objective measures of peripheral neurologic conditions
- Multiple sclerosis
- Mortality from cardiovascular disease or parasitic diseases
- Decreased lung function
- Mortality due to mechanical trauma or other external causes

multitude of symptoms seen in Gulf War illness, and it is unlikely that a single definitive causal agent will be identified this many years after the war.

A further problem is that most of the studies have excluded the psychological aspects of Gulf War illness with regard to both diagnosis and treatment. This is despite the fact that veterans have reported symptoms such as chronic pain and sleep disturbances that may be amenable to psychological therapies, alone or in conjunction with other treatments. Animal studies that attempt to mirror Gulf War illness have been of little use because it is difficult to establish experimental exposures that are representative of those experienced by Gulf War veterans during deployment.

Recommendation: Any future studies of Gulf War illness should recognize the connections and complex relationships between brain and physical functioning and should not exclude any aspect of the illness with regard to improving its diagnosis and treatment.

Emerging diagnostic technologies and personalized approaches to medical care offer promise for the conduct of sufficiently powered research on the diagnosis and treatment of Gulf War illness.

Recommendation: The Department of Veterans Affairs and the Department of Defense should develop a joint and cohesive strategy on incorporating emerging diagnostic technologies and personalized approaches to medical care into sufficiently powered future research to inform studies of Gulf War illness and related health conditions.

This strategy should ensure that any future studies are scientifically rigorous, adequately powered, and optimize the likelihood of achieving meaningful and replicable findings. It should be informed by recognized subject matter experts and offer an opportunity for broad review and comment. Research support policies should be similarly developed to implement the strategy.

Neurologic Conditions

There was little new information pertaining to multiple sclerosis, Parkinson's disease, Alzheimer's disease, or migraines. Amyotrophic lateral sclerosis (ALS) is the only neurologic disease for which the committee found limited/suggestive evidence for an association with deployment to the Gulf War. Although Gulf War deployment was associated with increased odds of developing ALS and increased ALS severity, no association with ALS mortality (a uniformly fatal disease) was found. The committee concluded that further follow-up is warranted. The Gulf War veteran population is still young with respect to the development of other neurodegenerative diseases; therefore, the effects of deployment on their incidence and prevalence may not yet be obvious.

Recommendation: The Department of Veterans Affairs should continue to conduct follow-up assessments of Gulf War veterans for neurodegenerative diseases that have long latencies and are associated with aging; these include amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease.

Lung and Brain Cancer

The new studies identified by the committee found no statistically significant increase in the risk of brain cancer in deployed Gulf War veterans compared with their nondeployed counterparts. The studies indicate that the evidence for an association between deployment to the Gulf War and brain cancer is inadequate/insufficient.

Although prior committees found no evidence that Gulf War veterans were at increased risk for lung cancer in the approximately 10–15 years after the war, this committee notes that that time period may not have been adequate to account for the long latency of this disease. One large study of Gulf War veterans found an increased incidence of lung cancer based on state and VA cancer registry data from 1991 to 2006 for deployed versus nondeployed veterans, but neither veteran group had a greater risk when compared with the general population, and the study did not adjust for smoking status.

Thus, the Volume 10 committee finds that there continues to be inadequate/insufficient evidence to determine whether deployed Gulf War veterans are at increased risk of having any cancer, including lung canceer and brain cancer. The relative rarity of cancers such as brain cancer argues for studies with adequate power to detect them. This may require pooling data where feasible and the use of a variety of data sources such as state cancer registries.

Recommendation: The Department of Veterans Affairs should conduct further assessments of cancer incidence, prevalence, and mortality because of the long latency of some cancers. Such studies should maximize the use of cancer registries and other relevant sources, data, and approaches, and should have sufficient sample sizes to account for relatively rare cancers. These studies should also be able to report sex-specific and race/ethnicity-specific information.

Other Health Conditions

In contrast to cancer, the committee finds that sufficient time has elapsed to determine that Gulf War deployed veterans do not have an increased incidence of circulatory, hematologic, respiratory, musculoskeletal, gastrointestinal, genitourinary, reproductive, and chronic skin conditions compared with their nondeployed counterparts. The committee also recognizes that as Gulf War veterans age, it will be more difficult to differentiate the effects of deployment from the natural effects of aging on morbidity and mortality.

The committee finds that the association of deployment to the Gulf War with PTSD, anxiety disorders, substance abuse, and depression is well established, and further studies to assess whether there is an association are not warranted. The committee notes, however, that mental health conditions may be comorbid with other health outcomes such as cancer or neurodegenerative diseases.

There are no data on the delayed effects of Gulf War exposures, such as nerve agents and PB, to indicate that any amount of such toxicants that still remain in the body would be able to cause any adverse health effects this many years after exposure. Thus, the committee finds that, with the exception of diseases with long latency periods such as cancer, it is not reasonable to expect increased risks of these other diseases.

Recommendation: Further studies to assess the incidence and prevalence of circulatory, hematologic, musculoskeletal, gastrointestinal, genitourinary,

reproductive, endocrine and metabolic, respiratory, chronic skin, and mental health conditions due to deployment in the Gulf War should not be undertaken. Rather, future research related to these conditions should focus on ensuring that Gulf War veterans with them receive timely and effective treatment.

Exposure Assessments

Given the likelihood that recall bias will increase with time, the committee finds that collecting further self-reported exposure information from Gulf War veterans is not necessary. For future conflicts, however, collecting exposure information before, during, and after deployment, preferably using individual environmental monitoring devices and military health and administrative records to capture such information as vaccine administration, troop location, and toxicant concentrations, will permit a more accurate assessment of actual exposures.

The committee also finds that efforts to model or otherwise reconstruct the exposures that Gulf War veterans experienced during deployment are also unlikely to yield useful results. Although animal models of Gulf War illness may be helpful in identifying markers of illness or treatment, the applicability of those laboratory exposures to the real-world exposures of veterans will continue to be unknown. Little credible exposure information currently exists for U.S. Gulf War veterans (except for depleted uranium).

Recommendation: Without definitive and verifiable individual veteran exposure information, further studies to determine cause-and-effect relationships between Gulf War exposures and health conditions in Gulf War veterans should not be undertaken.

Sex, Race, and Ethnicity

An unprecedented number of women deployed to the Gulf War (almost 50,000), but few data are available on the health of those women. Women may have different responses to stress and other exposures and, thus, may have different health effects. Therefore, it is important to assess and report on their health conditions so patterns over time can be understood and used to improve their health and potentially avoid similar problems in the future.

Similarly, health risks for racial/ethnic minority veterans as a result of deployment may also be different. Genetic risks for some diseases vary across race and ethnicities; for example, blacks are at greater risk for developing heart disease than whites.

Notwithstanding well-known differences in disease profiles according to sex and race/ethnicity, few studies on Gulf War veterans specifically report outcomes for women or minorities, although many veteran studies adjust for sex and race/ethnicity in their analyses. This lack of distinction is important and makes it imperative that researchers report sex-specific and race/ethnicity-specific outcomes, particularly in large cohorts and where population subgroups may be oversampled.

Recommendation: Sex-specific and race/ethnicity-specific health conditions should be determined and reported in future studies of Gulf War veterans. In addition, selected prior studies (e.g., large cohort studies) should be reviewed to determine whether reanalysis of the data to assess for possible sex-specific and race/ethnic-specific health conditions is feasible.

MOVING FORWARD

Beginning with Volume 1 of the *Gulf War and Health* series, numerous IOM committees have reviewed the literature on the health of deployed and nondeployed Gulf War veterans. Although there have been some variations in the strength of the associations between specific exposures (e.g., combustion products, infectious agents, and sarin) and particular health outcomes, in general the results have been remarkably consistent. What is striking about this and prior Gulf War and Health committees' findings is that the health conditions found to be associated with Gulf War deployment are primarily mental health disorders and functional medical disorders. What links these conditions is that they have no objective medical diagnostic tests and are diagnosed based on subjective symptom reporting. These associations emphasize the interconnectedness of the brain and body.

The committee concludes that it is time research efforts move forward and focus on this interconnectedness when seeking to improve treatment of veterans for Gulf War illness. Further exploration of treatments and management strategies for the symptoms of Gulf War illness, even in the absence of a definitive etiology, is warranted. VA and Department of Defense researchers have already conducted some clinical trials based on therapies that have previously shown benefits for conditions characterized by unexplained symptoms. Gulf War illness research should be realigned to focus on the treatment of the illness's complex symptomatology rather than its causal mechanisms. Such research should recognize the growing evidentiary base demonstrating the intricate and complex brain–body relationship. The acute response to an exposure that causes stress (physiologic or psychologic) involves interactions and effects among multiple organ systems in the body, including the brain, gut, heart, liver, immune system, thyroid, adrenals, pituitary, gonads, bone, and skin. The multisystem effects may be profound and long lasting. To ignore available treatments that may improve the functioning of any of these organ systems would be to do a disservice to our Gulf War veterans.

Recommendation: Future Gulf War research should place top priority on the identification and development of effective therapeutic interventions and management strategies for Gulf War illness. The Department of Veterans Affairs should support research to determine how such treatments can be widely disseminated and implemented in all health care settings.

1

INTRODUCTION

In response to the invasion of Kuwait by Iraq in August 1990, the United States led a coalition of 34 countries, including the United Kingdom, Australia, Canada, France, and Denmark, in a buildup of forces in the Persian Gulf called Operation Desert Shield. This multinational effort was followed by Operation Desert Storm, which began in January 1991 with an air offensive and a 4-day ground war. The war was over by the end of February, and a ceasefire was signed in April 1991. Over the course of the buildup and war, almost 700,000 U.S. troops were deployed to the Persian Gulf region, although by June 1991 only about 50,000 U.S. troops remained in the area. Although brief with relatively few injuries and deaths among the coalition forces, the legacy of the war has been a large contingent of veterans who suffer from a number of health problems that have persisted for over 25 years.

Prior to and during the Gulf War, the service members who were deployed to the theater of conflict were exposed to many hazardous agents and situations, both known and unknown, many of which were unique to that conflict. Because Iraq had been known to use chemical and possibly biological agents against its own people and others, many service members received mandatory vaccines to prevent anthrax and botulism. Pyridostigmine bromide (PB) was first used as a prophylaxis against potential nerve agent exposure. Previous conflicts had not included exposures to depleted uranium in munitions. Other known exposures ranged from oil-well fire smoke, to dust and excessive heat, to pesticides. While some of these exposures were documented, many were not; the exposures experienced by service members were numerous and highly variable.

During and after the Gulf War, veterans began reporting a variety of health problems, particularly a constellation of symptoms that have been termed Gulf War illness. These symptoms continue to plague as many as a third of the veterans who were deployed to the Persian Gulf region. Furthermore, these symptoms are seen in veterans from several of the countries that formed the coalition forces. Numerous researchers have studied the variety of health outcomes presented by Gulf War veterans and attempted to identify possible exposures that may have caused or contributed to those outcomes.

THE GULF WAR SETTING[1]

The section provides background for the numerous Institute of Medicine (IOM) committees that have attempted to determine what health effects may be expected from the

[1] This section is adapted from *Gulf War and Health,* Volumes 1, 2, 4, 6, and 8 (IOM, 2000, 2003, 2006b, 2008b, 2010).

myriad exposures that Gulf War veterans received during their deployments. In particular, it focuses on the environment of the Persian Gulf and the many natural and anthropogenic exposures that the Gulf War veterans, particularly U.S. service members, may have experienced. Some exposures were unique to the Gulf War such as the numerous oil-well fires and their smoke, the release of the nerve agents sarin and cyclosarin, and the use of PB as a prophylaxis for the nerve agents. Other exposures, such as vaccinations against anthrax and botulinum, while uncommon, have been used in other wars, including the recent conflicts in Iraq and Afghanistan. A discussion of the possible health effects of Gulf War service, however, involves many complex issues, some of which are explored below. These issues include exposure to multiple biologic and chemical agents, multiple exposures to those agents, a dearth of environmental sampling data collected during or modeled after deployment, and individual variability factors.

Deployment and Demographics

The buildup for the Gulf War was extremely rapid. Within 5 days after Iraq invaded Kuwait in August 1990, Operation Desert Shield began with U.S. troops moving into the Persian Gulf region. In less than 2 months, over 150,000 U.S. service members, including nearly 50,000 reservists, were in the region, and in October 1990, another 60,000 troops had arrived in the region followed by an additional 135,000 reservists and National Guard members in November. Of the 697,000 U.S. troops deployed in the Gulf War, the peak number there at any one time was about 560,000. The 1990–1991 Gulf War reflected many changes from previous wars, particularly in the demographic composition of military personnel. Military personnel were, overall, older than those who had participated in previous wars with a mean age of 28 years. Compared with any prior force in U.S. history, those deployed to the Persian Gulf region were also more ethnically diverse; 70% of the troops were non-Hispanic/white; 23% were black, and 5% were Hispanic (Joseph, 1997). They also comprised more women (almost 7%), parents, and activated members of the Reserves and National Guard (about 17% or 106,000) who were temporarily uprooted from their civilian lives (VA, 2011).

Combat Experiences

Combat is widely acknowledged to be one of the most intense experiences that a person can have and may include many threatening situations such as killing or attempting to kill an enemy; being shot at by others; exposure to dead and wounded comrades, enemy combatants, and civilians; and being injured. Although the Gulf War was relatively short and involved few deaths and casualties, there were numerous opportunities for exposure to potentially harmful situations during deployment. These situations included being in the vicinity of Scud missile explosions, contact with prisoners of war, direct combat duty, coming under small-arms fire, having artillery close by (Kang et al., 2000; Unwin et al., 1999), and fear of terrorist or chemical attacks. Many surveys have been conducted to assess Gulf War veterans' combat experiences and exposures, and in nearly all of them, veterans have reported exposure to a wide variety of threatening or harmful situations during their deployments.

Living Conditions

Combat troops were crowded into warehouses and tents upon arrival in the gulf region and then often moved to isolated desert locations. Most troops lived in tents and slept on cots

lined up side by side, affording virtually no privacy or quiet. Sanitation was often primitive, with strains on latrines and communal washing facilities. Hot showers were infrequent, the interval between laundering uniforms was sometimes long, and desert flies were a constant nuisance, as were scorpions and snakes. Military personnel worked long hours and had narrowly restricted outlets for relaxation. Troops were ordered not to fraternize with local people, and alcoholic drinks were prohibited in deference to religious beliefs in the host countries. A mild traveler's type of diarrhea affected more than half of the troops in some units. Fresh fruits and vegetables from neighboring countries were identified as the cause and were removed from the diet. Thereafter, the diet consisted mostly of packaged foods and bottled water.

For the first 2 months of troop deployment (August and September 1990) the weather was extremely hot, with air temperatures as high as 115°F and sand temperatures reaching 150°F. Except for coastal regions, the relative humidity was less than 40%. Troops had to drink large quantities of water to prevent dehydration. Although the summers were hot and dry, temperatures in winter were low, with windchill temperatures at night dropping to well below freezing. Wind and blowing sand made protection of skin and eyes imperative. Goggles and sunglasses helped somewhat, but visibility was often poor.

Psychological Stressors

Deployment to a war zone and combat exposure can result in psychological as well as physical stressors for service members. Rapid mobilization exerted substantial pressure on those who were deployed, disrupting lives and separating families. Uncertainty about the duration of deployment was a continuing concern for U.S. troops during the Gulf War, particularly during the early phases of the buildup. This conflict, unlike the earlier Vietnam War, mobilized large numbers of reserve and National Guard units. For these troops, there was the added uncertainly about whether their jobs would be available when they returned to civilian life (VA, 2011). Although this conflict had better mechanisms for and access to communication with family in the United States, deployment could add to the stress of maintaining family relationships, particularly for reserve and National Guard personnel who may not have deployed with a familiar or cohesive unit.

The veterans also experienced other psychological stressors typically associated with combat and deployment such as uncertainty about the presence of chemical and biological agents, seeing dead or wounded combatants and civilians, and fear of attack by opposition forces. Women and men who deployed to the Gulf War theater in 1990–1991 experienced many of the same exposures and stressors. Although women were not allowed to serve in combat specialties, they were deployed in combat-support roles as administrators, air-traffic controllers, logisticians, ammunition technicians, engineering-equipment mechanics, ordnance specialists, communicators, radio operators, drivers, law-enforcement specialists, aviators, and guards. Still others served on hospital, supply, oiler, and ammunition ships or served as public affairs officers and chaplains (DoD, 2004). Female military personnel were more likely to experience sexual harassment and assault than male personnel (Wolfe et al., 1998). In one survey of deployment experiences, although men and women reported similar exposure to most stressors, women reported more exposure to interpersonal stressors, such as incidents of sexual harassment, and less postdeployment social support. Men reported more mission-related stressors, such as combat experiences (Vogt et al., 2005). The effects of these psychologic stressors are discussed in more depth in *Gulf War and Health, Volume 6* (IOM, 2008b).

Environmental and Chemical Exposures

During their deployment to the Persian Gulf, service members had a variety of environmental exposures related to their deployment such as solvents, fumes from kerosene heaters, vaccines, and environmental exposures that resulted from the conflict itself, such as the depleted uranium (DU) used in munitions, excessive heat, and oil-well fire smoke. Some of the exposures were constant such as dust, heat, and pesticides, while other exposures were intermittent or infrequent such as PB or DU.

Oil-Well Fire Smoke

The most visually dramatic environmental event of the Gulf War was the smoke from more than 750 oil-well fires in Kuwait. Smoke plumes from individual fires rose and combined to form giant plumes that could be seen for hundreds of kilometers. As noted in earlier *Gulf War and Health* volumes, it has been difficult to correlate veterans' self-reports of exposure to the smoke with dispersion models based on troop location information (IOM, 2006b). Health outcomes associated with exposure to the smoke from the Kuwaiti oil well fires are discussed in Volume 3 of the *Gulf War and Health* series (IOM, 2005).

Fuels, Combustion Products, and Propellants

There were additional potential sources of exposure to petroleum-based combustion products. Kerosene, diesel, and leaded gasoline were used in unvented tent heaters, cooking stoves, and portable generators. Exposures to tent-heater emissions were not specifically documented, but a simulation study was conducted after the war to determine exposure (Cheng et al., 2001). Petroleum products, including diesel fuels, were also used to suppress sand and dust, and petroleum fuels were used to aid in the burning of waste and trash in open air burn pits. Combustion products may contain many hazardous agents such as polyaromatic hydrocarbons, dioxins, furans, and methane. Health outcomes associated with exposure to the combustion products from the Gulf War region are discussed in Volume 3 of the *Gulf War and Health* series (IOM, 2005).

Pesticides

Pesticide use was widespread among troops in the Persian Gulf region to combat the region's ubiquitous insect and rodent populations. Although guidelines for the use of the pesticides were strict, there were many reports of misuse, including U.S. troops wearing dog flea collars. The pesticides used included methyl carbamates (e.g., proxpur, carbaryl), organophosphates (e.g., chlorpyrifos, diazinon, malathion), pyrethroids, lindane, chlorinated hydrocarbons, and the insect repellant DEET (*N,N*-diethyl-3-methylbenzamide). The use of those pesticides is covered in several reports (for example, DoD, 2001; RAND, 2000), however, objective information regarding individual levels of pesticide exposure is generally not available, and reports by individual veterans as to their use of and possible exposure to pesticides are subject to considerable recall bias. Health outcomes associated with exposure to the insecticides used in the Gulf War are discussed in Volume 2 of the *Gulf War and Health* series (IOM, 2003).

Solvents and Other Occupational Exposures

Many exposures could have been related to particular occupational activities in the Gulf War. The majority of occupational chemical exposures appear to have been related to repair and maintenance activities, including battery repair (corrosive liquids), cleaning and degreasing

(solvents, including chlorinated hydrocarbons), sandblasting (abrasive particles), vehicle repair (i.e., carbon monoxide and organic solvents), weapon repair (lead particles), and welding and cutting (chromates, nitrogen dioxide, and heated metal fumes). In addition, troops painted vehicles and other equipment used in the gulf with a chemical-agent-resistant coating either before being shipped to the gulf or at ports in Saudi Arabia. Working conditions in the field were not ideal, and recommended occupational-hygiene standards might not have been followed at all times. Health outcomes associated with exposure to the solvents used in the Gulf War are discussed in Volume 2 of the *Gulf War and Health* series (IOM, 2003).

Depleted Uranium

Exposure of U.S. personnel to DU occurred as the result of friendly-fire incidents, cleanup operations, and accidents (including fires). Other personnel might have inhaled DU dust through contact with DU-contaminated tanks or munitions. Assessment of DU exposure, especially high exposure, is considered to be more accurate than assessment of exposure to most other agents because of the availability of biologic monitoring information. Health outcomes associated with exposure to the DU used in the Gulf War are discussed in Volume 1 of the *Gulf War and Health* series (IOM, 2003) and in *Updated Literature Review of Depleted Uranium* (IOM, 2008a).

Threat of Chemical and Biologic Warfare

When U.S. troops arrived in the Persian Gulf region, they had no way of knowing whether they would be exposed to biologic and chemical weapons. Iraq previously had used such weapons in fighting Iran and in attacks on the Kurdish minority in Iraq. Military leaders feared that the use of such weapons in the gulf could result in the deaths of tens of thousands of U.S. troops. Prophylactic measures were instituted to help address this uncertainty.

Pyridostigmine Bromide

Troops were given blister packs of 21 tablets of PB to protect against agents of chemical warfare, specifically nerve gas; the recommended dosage was one 30-mg tablet every 8 hours. They were to take PB on the orders of a commanding officer when a chemical-warfare attack was believed to be imminent. Chemical sensors and alarms were distributed throughout the region to warn of such attacks. The alarms were extremely sensitive and could be triggered by many substances, including some organic solvents, vehicle exhaust fumes, and insecticides. Alarms sounded often and troops responded by donning the confining protective gear and ingesting PB as an antidote to nerve gas. In addition to the alarms, there were widespread reports of dead sheep, goats, and camels, which troops were taught could be indication of the use of chemical or biologic weapons. The sounding of the alarms, the reports of dead animals, and rumors that other units had been hit by chemical warfare agents caused them to be concerned that they would be or had been exposed to such agents. Fricker et al. (2000) estimated that at least half of the deployed troops took PB pills at some time during their deployments. Health outcomes associated with exposure to PB are discussed in Volume 1 of the *Gulf War and Health* series (IOM, 2000).

Nerve Agents

Despite the small numbers of U.S. personnel injured or killed during combat in the Gulf War, the troops, as in any war, faced the fear of death, injury, or capture by the enemy. After the

war, there was the potential for other exposures, including U.S. demolition of a munitions storage complex at Khamisiyah, Iraq, which—unbeknownst to demolition troops at the time—contained stores of sarin and cyclosarin. The potential exposures to sarin and cyclosarin from the Khamisiyah incident have been the subject of several modeling and health outcome studies. Depending on the dispersion model used to estimate the sarin and cyclosarin plume and troop unit locations, the number of Gulf War veterans who may have been exposed to the nerve agents ranged from an initial estimate of 10,000 troops within 25 km of Khamisiyah in a 1997 model, to more than 100,000 troops using a 2000 model. However, more than 35,000 troops originally considered to have been exposed and notified that they may have been within the plume were subsequently considered to have been unexposed and 37,000 troops were newly identified as being in the hazard area (IOM, 2006b), adding to the confusion of how many troops were actually exposed to nerve agents and at what levels. As stated in *Volume 4* "No medical reports by the US Army Medical Corps at the time of the release were consistent with signs and symptoms of acute exposure to sarin" (IOM, 2006b). Health outcomes associated with exposure to sarin and cyclosarin are discussed in Volume 1 of the *Gulf War and Health* series (IOM, 2000) and in *Gulf War and Health: Updated Literature Review of Sarin* (IOM, 2004).

Vaccines

U.S. Gulf War troops received standard vaccinations before military deployment, such as cholera, meningitis, rabies, tetanus, and typhoid. In addition, about 150,000 troops received anthrax vaccine and about 8,000 troops received botulinum toxoid vaccine. As noted in Volume 1, "Medical records from the Gulf War contain little or no information about who received these vaccines, how frequently the vaccines were administered, or the timing of vaccinations relative to other putative exposures." Health outcomes associated with the vaccines given to U.S. troops in the Gulf War are discussed in Volume 1 of the *Gulf War and Health* series (IOM, 2000).

THE GULF WAR AFTERMATH

Although Operation Desert Storm was relatively short, Operation Desert Shield, the buildup of troops and equipment in the Persian Gulf region, and the aftermath of the war went on for many months. Even before the war was over, U.S. and coalition troops began complaining of a constellation of symptoms such as headaches, muscle aches, sleep disturbances, and fatigue. The mix of symptoms and the variability of their severity made it difficult to associate the health problems with a specific cause or exposure prior to or during the service member's deployment. Upon their return to the United States, many veterans reported their complaints to the Department of Defense (DoD) and the Department of Veterans Affairs (VA). Initial studies indicated that similar symptoms were being experienced by service members from the coalition forces as well. Some veterans began calling their symptoms "Gulf War Illness" or "Gulf War syndrome," and it has become the signature health legacy of the war. Given the numerous symptoms and the multiple exposures, DoD and VA were slow to react to the influx of sick veterans. The persistence of the symptoms and their impact on the veterans' quality of life, prompted veterans and veteran service organizations to seek the assistance of Congress in getting treatment and compensation.

Of the many specific health outcomes that have (or have not) been associated with deployment to the Persian Gulf region, one of the most common adverse effects experienced by Gulf War veterans compared with their nondeployed counterparts is poor general health that

results in decreased functioning and quality of life. Virtually all surveys of Gulf War veterans, whether taken shortly after the war or years later, indicate that Gulf War veterans, particularly those with Gulf War illness or posttraumatic stress disorder, frequently experience decreased physical and mental functioning and reduced quality of life (Voelker et al., 2002; Proctor et al., 2001a; Hoptof et al., 2003a; Toomey et al., 2007) and that these issues have persisted long after the war (Li et al., 2011a; Sim et al., 2015). Poor health status can have long-term ramifications such as emotional and behavioral problems, which in turn can often lead to social and economic challenges including substance abuse. Assessing the psychosocial problems of Gulf War veterans using latent indicators such as unemployment, family instability, and homelessness may be as important as addressing their health problems (Rao et al., 2009; Robertson, 2008; Walker et al., 2007).

Legislative Actions

In 1998, in response to the growing concerns of Gulf War veterans, Congress passed two laws: P.L. 105-277, the Persian Gulf War Veterans Act, and P.L. 105-368, the Veterans Programs Enhancement Act. The goals of those laws were to attempt to identify what health outcomes might be expected from the environmental agents to which veterans had been exposed during their deployments, and called on VA to treat those health outcomes. The laws did not mention the presence of a "Gulf War illness," nor did they require that VA or any other organization determine the cause of the symptoms that veterans were experiencing.

Those laws directed the secretary of veterans affairs to enter into a contract with the National Academy of Sciences (NAS) to review and evaluate the scientific and medical literature regarding associations between illness and exposure to toxic agents, environmental or wartime hazards, or preventive medicines or vaccines associated with Gulf War service and to consider the NAS conclusions when making decisions about compensation. The study was assigned to the IOM, which is now part of the National Academies of Sciences, Engineering, and Medicine.

The Persian Gulf War legislation directs the IOM to study diverse biologic, chemical, and physical agents. Exposures to many of the Gulf War agents have been extensively studied and characterized, primarily in occupational settings (for example, exposure to pesticides, solvents, and fuels), but exposures to others have not been as well studied and characterized in human populations (for example, exposure to nerve agents and oil-well fire smoke).

The Veterans Programs Enhancement Act of 1998 (P.L. 105-368) established the federal Research Advisory Committee on Gulf War Veterans' Illnesses (RAC). The RAC, which includes researchers who are studying the health of these veterans, clinicians who have treated them, and members of the general public (including veterans), has published several reports on the scientific literature on Gulf War veterans. The most recent report, published in 2014, also includes recommendations for future research efforts on illnesses affecting Gulf War veterans (RAC, 2014).

Institute of Medicine Reports

The IOM has prepared numerous studies on the health of Gulf War veterans. As a result of the 1998 legislation, the IOM has conducted more than 10 *Gulf War and Health* and related studies to look at the veterans' exposures identified in the legislation and the health effects that might be associated with those exposures. Given the large number of agents to study, IOM divided the task into several reports:

Gulf War and Health, Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines (IOM, 2000)
Gulf War and Health, Volume 2: Insecticides and Solvents (IOM, 2003)
Gulf War and Health, Volume 3: Fuels, Combustion Products, and Propellants (IOM, 2005)
Gulf War and Health: Updated Literature Review of Sarin (IOM, 2004)
Amyotrophic Lateral Sclerosis in Veterans: Review of the Scientific Literature (IOM, 2006a)
Gulf War and Health, Volume 4: Health Effects of Serving in the Gulf War (IOM, 2006b)
Gulf War and Health, Volume 5: Infectious Diseases (IOM, 2007)
Gulf War and Health, Volume 6: Physiologic, Psychologic, and Psychosocial Effects of Deployment-Related Stress (IOM, 2008b)
Gulf War and Health, Volume 7: Long-Term Consequences of Traumatic Brain Injury (IOM, 2009)
Gulf War and Health, Volume 8: Update of Health Effects of Serving in the Gulf War (IOM, 2009)
Gulf War and Health, Volume 9: Long-term Effects of Blast Exposures (IOM, 2014b)

As part of the *Gulf War and Health* series, IOM also prepared the reports *Gulf War and Health: Updated Literature Review of Sarin* (IOM, 2004), *Updated Literature Review of Depleted Uranium* (IOM, 2008a), and *Treatment for Chronic Multisymptom Illness* (IOM, 2013).

Although not part of the *Gulf War and Health* series, the IOM has prepared other reports on Gulf War veterans. In the 1996 report *Health Consequences of Service During the Persian Gulf War: Recommendations for Research and Information Systems*, the IOM was asked to review how DoD and VA collected and maintained data on Gulf War veterans and how that data might be used (IOM, 1996). The DoD and VA asked the IOM to assess important health issues in Gulf War veterans and design a study to address those issues in the 1999 report *Gulf War Veterans: Measuring Health* (IOM, 1999). In 2001, the IOM prepared the *Gulf War Veterans: Treating Symptoms and Syndromes*, and in 2012, it was asked by VA to establish a case definition for chronic multisymptom illness (IOM, 2014a), also known as Gulf War illness or Gulf War syndrome. Finally, the IOM (2015) recently completed *Consideration for Designing an Epidemiologic Study of Multiple Sclerosis and Other Neurologic Disorders in Pre and Post 9/11 Gulf War Veterans*.

Beginning with Volume 1 of the *Gulf War and Health* series, IOM committees developed a process for assessing the evidence for each study and reaching conclusions regarding the weight of the evidence for each exposure or environmental agent and possible health outcomes. Because each committee was composed of different experts and the exposures varied for each report, each committee made slight modifications to the assessment process. Each committee's approach is typically discussed at some length in the methods chapter of its report.

Although the first three volumes of the *Gulf War and Health* series dealt with specific environmental agents, in 2005, VA requested that the IOM appoint a committee to review the medical literature and to summarize what was known about the then current status of veterans' health. In 2006, the committee produced a report, *Gulf War and Health, Volume 4: Health Effects of Serving in the Gulf War* that summarized the overall health effects in veterans and noted which health outcomes were more evident in veterans who had deployed to the Persian Gulf region compared with their nondeployed counterparts, irrespective of the specific exposures

experienced by the deployed veterans. The Volume 8 report was an update of Volume 4, covering the literature published between 2006 and 2009 on the health effects seen in deployed and nondeployed veterans. Volume 10 is a further update of the medical literature on Gulf War veterans' health from 2009 through 2015.

Department of Veteran Affairs' Response

In response to each of the IOM *Gulf War and Health* reports, the secretary of the Department of Veterans Affairs is required to "determine whether or not a presumption of service connection is warranted for each illness, if any, covered by the [NAS] report" (P.L. 105-277). As of July 2011, VA policy (VA, 2015a) stated:

> VA presumes certain chronic, unexplained symptoms existing for 6 months or more are related to Gulf War service without regard to cause. These "presumptive" illnesses must have appeared during active duty in the Southwest Asia theater of military operations or by December 31, 2016, and be at least 10 percent disabling. These illnesses include:
>
> - **Chronic fatigue syndrome**, a condition of long-term and severe fatigue that is not relieved by rest and is not directly caused by other conditions.
> - **Fibromyalgia,** a condition characterized by widespread muscle pain. Other symptoms may include insomnia, morning stiffness, headache, and memory problems.
> - **Functional gastrointestinal disorders**, a group of conditions marked by chronic or recurrent symptoms related to any part of the gastrointestinal tract. Functional condition refers to an abnormal function of an organ, without a structural alteration in the tissues. Examples include irritable bowel syndrome (IBS), functional dyspepsia, and functional abdominal pain syndrome.
> - **Undiagnosed illnesses** with symptoms that may include but are not limited to abnormal weight loss, fatigue, cardiovascular disease, muscle and joint pain, headache, menstrual disorders, neurological and psychological problems, skin conditions, respiratory disorders, and sleep disturbances.

Based on the previous 2006 and 2010 IOM reports, VA has established presumptions for service connection for amyotrophic lateral sclerosis for veterans who have 90 or more days of continuous active military service, for posttraumatic stress disorder if it is associated with an in-service stressful event, and for nine infectious diseases, specifically malaria, brucellosis, *Campylobacter jejuni*, *Coxiella burnetii* (Q fever), tuberculosis, nontyphoid *Salmonella*, *Shigella*, visceral Leishmaniasis, and West Nile virus. None of the other health outcomes associated with exposures experienced during deployment to the 1990–1991 Gulf War, as identified in the IOM *Gulf War and Health* series, are presumed to have service connection at this time, although veterans may still seek to establish service connection individually for diseases and illnesses associated with their service in the Gulf War.

CHARGE TO THE COMMITTEE

The charge to the Volume 4 and Volume 8 committees and to the current committee is different from charges to other IOM Gulf War and Health committees in that these three committees were not asked to associate health outcomes with specific biologic, chemical, or other agents believed to have been present in the Persian Gulf region, but rather to examine health outcomes related to deployment to the gulf region as a whole. The specific charge to the current committee, as requested by VA, is to

> comprehensively review, evaluate, and summarize the available scientific and medical literature regarding health effects in the 1990–1991 Gulf War veterans. The committee will pay particular attention to neurological disorders (e.g., Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, and migraines), cancer (especially brain cancer and lung cancer), and chronic multisymptom illness. The proposed study will update earlier IOM reviews on *Gulf War and Health*, and this volume (Volume 10) will update the literature since the publication of the 2006 (Volume 4) and 2010 (Volume 8) *Gulf War and Health* reports. The committee will also provide recommendations for future research efforts on Gulf War veterans.

The committee was not asked to and did not attempt to determine the cause of or treatment for Gulf War illness. The committee also did not concern itself with any policy issues, such as potential costs of compensation or policies regarding compensation, nor did it evaluate VA practices.

COMMITTEE'S APPROACH TO ITS CHARGE

The committee began its task by holding two public sessions. At those sessions, the committee heard from representatives of VA and from Gulf War veterans about their health outcomes that have persisted for the past 25 years, particularly the symptoms associated with Gulf War illness. The committee also heard presentations from representatives of the RAC, who discussed that committee's findings and recommendations and from several researchers who have been studying Gulf War illness. Those sessions helped the committee to put its efforts in context and to clarify an approach to its task.

In addition to the public sessions, the committee conducted extensive searches of the epidemiologic literature published since 2009 (the date of the last literature search for Volume 8) using the same search strategy as that used for Volume 4 and Volume 8. In an effort to be comprehensive, literature searches were also conducted to look for animal models of Gulf War illness or toxicologic (animal) studies where the animals were exposed to a mixture of agents that attempted to simulate those experienced by Gulf War veterans during deployment. Details of the literature search strategy and criteria for selection of relevant studies are discussed in Chapter 2, "Considerations in Identifying and Evaluating the Literature."

Each of these literature review committees recognized that its members needed to have an appreciation of the Gulf War experience, including the magnitudes of possible exposures for all the armed forces that served in the gulf, including those deployed to the region after the war ended. Therefore, in addition to reviewing studies on U.S. troops, this and prior committees

reviewed studies of Gulf War veterans from Australia, Canada, Denmark, the United Kingdom, and Kuwait, where available.

To be comprehensive in its approach to the epidemiologic literature, the committee defined its body of evidence to include studies reviewed in Volume 8 (which also assessed those studies cited in Volume 4) and any new studies identified in the literature search or submitted to the committee. Once the committee had considered the studies cited in Volume 8 and evaluated the new studies identified from the updated literature, it also considered whether there were other studies that provided useful background information or otherwise informed the committee's deliberations. The committee reviewed the entire body of relevant literature using a weight-of-the-evidence approach and determined the strength of the association between being deployed to the Gulf War and a specific health condition. Throughout this process, many tangential but relevant and informative studies were identified, such as those using neuroimaging techniques or genetic markers to assess aspects of Gulf War illness; they are briefly discussed in each relevant section as "Other Related Studies."

ORGANIZATION OF THE REPORT

Chapter 2 provides the committee's methods for choosing and evaluating the epidemiologic and other studies that are reviewed in later chapters and its weight of the evidence approach. Chapter 3 describes the major epidemiologic studies that have been conducted on Gulf War veterans and provides information about the numerous studies that have been derived from them; the chapter includes a summary table that lists all the original Gulf War veteran cohort studies and their derivative studies. In Chapter 4, the committee considers the many health conditions that have been examined in deployed and nondeployed Gulf War veterans. For each health condition, the committee provides a summary of the literature that was described in Volumes 4 and 8 and any new relevant literature, and comes to a conclusion as to the strength of the association between deployment to the Gulf War and a health condition. Animal toxicity studies that have attempted to look at the etiology, mechanisms, and health outcomes associated with Gulf War exposures are presented in Chapter 5. Finally, in Chapter 6 the committee summarizes its findings with regard to the health of Gulf War veterans and makes recommendations for future research efforts to help diagnose and treat their many health conditions. Chapter 7 contains all the references cited in the previous chapters. Brief biographical sketches of the committee members are provided in the Appendix.

2

CONSIDERATIONS IN IDENTIFYING AND EVALUATING THE LITERATURE

This chapter presents the approach and methods that the Volume 10 committee used to identify and evaluate the scientific and medical literature on Gulf War veterans and the process used to reach the conclusions on the association between deployment to the Gulf War and a given health outcome. It provides information on how the committee searched the literature, and what evaluation criteria were used to screen and categorize the literature. The categories of association that were to draw conclusions about the possible health effects that might result from being deployed are then presented. Finally, the committee describes some of the issues it encountered when considering the literature on Gulf War exposures and health outcomes such as multiple exposures and individual variability. Because the Volume 10 committee closely followed the approach used by prior Gulf War and Health committees, particularly Volumes 4 and 8, much of the following information was previously described in Chapter 2 of Volume 8 (IOM, 2010).

IDENTIFICATION OF THE LITERATURE

The Volume 10 committee, while tasked with updating the earlier Volumes 4 and 8, also was asked to comprehensively review, evaluate, and summarize the scientific and medical literature on health effects seen in 1990–1991 Gulf War veterans. The committee began its work by overseeing extensive searches of the scientific literature, including published articles, other reports, and government documents that had been published since the last literature search conducted for Volume 8 in 2009. The updated search retrieved over 280 studies of potential relevance to this report. Studies that did not appear to have immediate relevance, based on an assessment of the title and abstract by committee members and Institute of Medicine (IOM) staff, were deleted from further consideration. Deleted studies included, but were not limited to, case reports, studies of civilians in the Persian Gulf region, treatments, short-term or acute health outcomes, rehabilitation, social outcomes (for example, employment), impacts on families, or studies of long-term outcomes from known physical events, such as gun-shot wounds. Removal of these studies yielded 76 potentially relevant studies to be considered and discussed by the committee. The studies obtained as full text were objectively evaluated by the committee members without preconceived ideas about what health outcomes might occur and what, if any, associations might be found between being deployed to the Gulf War and any health condition.

As discussed in more detail in Chapter 4, “Evaluation of Health Conditions,” many Gulf War veterans have experienced a multitude of symptoms—commonly including fatigue,

cognitive impairments, and chronic pain—that collectively has been termed Gulf War illness. Considerable research has focused on trying to identify what exposures might have caused Gulf War illness; a variety of causative exposures have been proposed, including pyridostigmine bromide (PB), pesticides, and the nerve agent sarin, individually or in some combination. Because this is the last volume in the *Gulf War and Health* series, the committee considered it prudent to look at the new literature on Gulf War illness, particularly animal models that attempt to simulate the multiple exposures experienced by Gulf War veterans during deployment. Therefore, an additional literature search was conducted to identify toxicologic and other animal studies that specifically sought to reproduce Gulf War exposures or describe a model of Gulf War illness. Because no prior IOM committee had conducted a comprehensive review of multiple Gulf War exposures but rather assessed exposures on a chemical-by-chemical or group of chemicals (e.g., carbamate pesticides) basis, this literature search was not limited by publication date.

The search of toxicologic literature identified over 100 papers. Committee members with the most experience in toxicology reviewed all titles and abstracts and selected 50 papers for further consideration. The selection criteria for those papers were that a study must have employed exposure levels and durations that were potentially representative of those of Gulf War veterans and that the studies must have included more than one chemical or other exposure; some studies looked at combinations of up to four exposures, such as PB, DEET, stress, and sarin, or PB, permethrin, and chlorpyrifos. The animal literature was reviewed by the committee's toxicologists and presented by them at the plenary sessions for discussion by the full committee.

EVALUATION PROCESS

The Volume 10 committee adopted a policy of using only published literature that had undergone rigorous peer review as the basis of its conclusions. While the process of peer review by fellow professionals increases the likelihood that high-quality studies will appear in the literature, it does not guarantee the validity of any particular study or the ability to generalize its findings. An exception to this policy was the inclusion of government reports and one government presentation.

The committee focused on epidemiologic studies in this report because epidemiology deals with the determinants, frequency, and distribution of disease in human populations rather than in individuals. In Chapter 4, "Evaluation of Health Conditions," three types of epidemiologic studies were used to support the committee's conclusions: cohort studies (including mortality studies), case-control studies, and cross-sectional studies. Volume 8 describes these major types of epidemiologic studies, the limitations inherent in conducting and using epidemiologic studies, how the committee used epidemiologic studies to make associations between deployment to the Gulf War and health conditions, and considerations in inferring causality from the available data. Case reports were not included in this report as the committee believes that while such reports may be interesting and provide unusual information, it is not appropriate to extrapolate findings from a single case to an entire population such as Gulf War veterans. Box 2-1 provides brief definitions of some of the terms used in the epidemiologic studies considered by this committee. The strength of an association between exposure and health condiiton is generally estimated quantitatively by using prevalence ratios, relative risks, odds ratios, correlation coefficients, or hazard ratios depending on the epidemiologic design

used. A ratio greater than 1.0 indicates that the outcome variable has occurred more frequently in the exposed group, and a ratio less than 1.0 indicates that it has occurred less frequently. Ratios are typically reported with a confidence interval (CI) to quantify random error. Statistical significance may be represented by a CI or a *p*-value. If the 95% CI for a risk estimate (such as an risk ratio or odds ratio) includes 1.0, the association is not considered to be statistically significant; however, if the interval does not include 1.0, the association is said to be statistically significant with an alpha error (likelihood that the association is due to chance) of 5% (that is, $p < 0.05$).

Box 2-1
Statistical Terms Used in This Report

Confidence interval (CI) is a range of values for the estimate within which the true value is thought to lie with a 95% level of confidence.

Hazard ratio (HR) is a ratio of the chance of an event occurring in one group compared to another group.

Incidence is the number of new cases of illness during a given period of time in a specified population.

Odds ratio (OR) represents the odds that an outcome will occur given a particular exposure compared to the odds of the outcome occurring in the absence of exposure. The measure approximates the relative risk when a disease is rare.

Prevalence is the number of existing cases of an illness or disease in a given population at a specific time or within a specified time period.

Proportional incidence ratio (PIR) is the ratio of the proportion of cases from a specified cause in the exposed group to that of the control group; usually used for cancer registries.

Proportionate mortality ratio (PMR) is the ratio of the proportion of deaths from a particular cause in the study population to that of the control group.

Relative risk (RR) is a general term used to denote the risk of a disease or outcome in a population with a given exposure compared to a population without the exposure. Relative risk may be described by a risk ratio, rate ratio, or odds ratio.

Standardized mortality ratio (SMR) is the ratio of the number of deaths observed in a study population to the number of deaths expected if the study population had the same mortality rate as the general population. The term "standardized" refers to adjustments made for age and sex differences between the study population and the general population.

Standardized incidence ratio (SIR) is the ratio of observed new cases of an outcome in the exposed cohort to expected number of new cases in the general population. The term "standardized" refers to adjustments made for age and sex differences between the study population and the general population.

Committee members having the most familiarity or expertise (e.g., neuroimaging, genetics, and toxicology) with a particular health condition reviewed all titles and abstracts and identified papers for full-text retrieval. Initially, the Volume 8 health conditions were used as the basis for the health conditions to be included in this volume, although other conditions would be included if suggested by the literature. One or more committee members then conducted a preliminary review of the relevant studies, including the studies cited in Volume 8, to determine if an individual study met the inclusion criteria for a primary or secondary study (see below) for a health condition. Each study was read critically and reviewed for its relevance and quality. The

responsible committee member(s) then presented the information from the preliminary screening and categorization to the full committee for discussion.

Typically, the information included a review of the Volumes 4 and 8 studies and conclusions, the methods used for selecting and evaluating the new study populations, the study results, and the committee member's assessment of the strengths and limitations of the study. Each primary and secondary paper was discussed for each health condition. Some of the larger cohort studies used a variety of methods and instruments to assess the health status of Gulf War veterans and it is for this reason that the committee discussed at some length the diagnostic approaches and use of self-reports for each paper. Because of the variability in the description and diagnosis of the health conditions considered in this report, the committee made no a priori assumptions about the usefulness of any paper for a health outcome; each paper was discussed individually for each health outcome (several papers assessed numerous health outcomes). The committee reviewed the studies in this report with a view to considering the level of random error, the potential for bias, as well as the authors' strategies for examining and/or limiting the effect of each on the study findings. Common types of biases found in the Gulf War veteran literature are identified in Box 2-2. For greater detail about epidemiology, biases, confounders and other methodological background, see Chapter 2 of Volume 8.

BOX 2-2
Common Medical-Research Biases That Affect Studies of Gulf War and Health

Selection bias: Bias can result from selection of participants in such a way that they do not represent the target population or the probability of selection is related to exposure or disease status. This may be due to a poor definition of the eligible population or failure to obtain a random sample. Includes

- *Nonresponse bias*: Participants have a different exposure or disease status from nonparticipants.
- *Volunteer bias*: Participants who volunteer are more likely to have the exposure or disease of interest; this is a particular problem for registry studies that collect information on participants who enroll voluntarily.
- *Healthy-warrior effect*: Veterans or personnel who were deployed may be healthier than those who were not deployed or than civilians; selection of healthier people occurs at enlistment and separation (ill and injured personnel are more likely to leave the military).

Information or measurement bias: Misclassification of participants' exposure or disease status may be based on the information collected by various methods (such as a mailed questionnaire, a telephone interview, record review, or a medical examination). Includes

- *Recall bias*: The presence of disease influences participants' reflection and perception of possible causes and can make them likely to report more exposures than or different exposures from nondiseased participants.
- *Reporting bias*: Participants are more likely to report responses that they perceive as favorable and to underreport undesirable responses.
- *Temporal ambiguity*: This occurs when it cannot be established that an exposure occurred before the onset of disease; it is common in cross-sectional assessments.

Confounding: This occurs when a risk factor for the disease that is also related to the exposure creates a spurious exposure–disease association; in other words, a risk factor may cause the exposed and nonexposed participants to have different background disease risks.

SOURCE: IOM (2014a).

After reviewing the updated literature, the committee agreed that some reorganization of the health conidtions was warranted for this volume; for example, women's health conditions are no longer considered in a separate section but rather are addressed in the section on each relevant health condition, and several outcomes were combined into one section, such as the inclusion of musculoskeletal disorders, fibromyalgia, chronic fatigue syndrome, and chronic widespread pain into one section on pain-related disorders.

After the studies had been discussed in plenary session, the responsible committee member(s) drafted the text for that health condition. The evidence tables were revised to include the new primary studies as well as the primary studies from Volumes 4 and 8; secondary studies were not included in the evidence tables. If there were no new primary studies for a health outcome, the evidence table from Volume 8 was included but not updated. Data and units are presented as reported in the cited studies, except where otherwise noted. The committee did not collect original data, nor did they perform any secondary data analyses such as meta-analyses.

The draft text was reviewed and discussed in further plenary sessions until all committee members reached a consensus on the description of the studies and the conclusions for each health outcome. After this language was agreed upon, the full committee assigned a category of association (discussed later in this chapter) based on the weight of the evidence (including the studies cited in Volume 4 and Volume 8, as well as any new studies) and expert judgment. It should be noted that the committee did not use a formulaic approach as to the number of primary and secondary studies that would be necessary to assign a specific category of association. Rather the committee's review required a thoughtful and nuanced consideration of all the studies as well as expert judgment, and this could not be accomplished by adherence to a narrowly prescribed formula of what data would be required for each category of association or for a particular health outcome.

Although the majority of the studies considered by the committee for this report were epidemiologic, other types of studies—such as animal toxicology, neuroimaging, functioning, and genetics—were assessed. The committee did not evaluate studies of acute trauma, rehabilitation, medical treatment, or transient illness. The committee also did not consider health outcomes seen in veterans of conflicts other than the Gulf War unless those veterans formed an appropriate control group (for example, veterans who had served in Bosnia).

Primary Studies

Primary studies provide the basis for the committee's findings. For a study to be included in the committee's review as primary it had to meet specified criteria. It had to be published in a peer-reviewed journal or other rigorously peer-reviewed publication, such as a government report or monograph. It also needed to (1) include sufficient detail to demonstrate rigorous methods (for example, had a control or reference group, and adjusted for confounders when needed); and (2) include information regarding a persistent health outcome, and use appropriate laboratory testing, if applicable. Furthermore, a primary study was considered to be generalizable to and representative of the Gulf War veteran population. Although the responsible committee member initially presented his or her determination of whether a study met the criteria, the committee discussed the study's methods and results using the inclusion criteria at some length before agreeing as to whether the study should be classified as primary.

For medical conditions that have no morphological features, the use of validated symptom criteria, such as those of the Rome Foundation for irritable bowel syndrome, are

preferred over reports of medical symptoms or group of symptoms. As noted earlier, for a study to be considered primary, it needed to have an independent assessment of an outcome rather than self-reports of an outcome or reports by family members, even if the self-report was of a "doctor-diagnosed" illness. Health effects should have been diagnosed or confirmed by a clinical evaluation, imaging, hospital record, or other medical record. For psychiatric outcomes, standardized interviews were preferred, such as the Structured Clinical Interview for the DSM-IV-TR (*Diagnostic and Statistical Manual of Mental Disorders-IV-TR*), the Diagnostic Interview Schedule, and the Composite International Diagnostic Interview. Similarly, for neurocognitive outcomes, standardized and validated tests were preferred. Additionally, outcomes had to be diagnosed after deployment and have an appropriate follow-up or latency period for the development of the health effect. The committee notes that the diagnostic criteria for and definitions of many of the health conditions considered in this report, such as mental health disorders, fibromyalgia, and chronic fatigue syndrome, have evolved over time and will continue to do so. However, the new definitions and criteria have not been applied to the studies discussed in this volume.

Secondary Studies

Studies reviewed by the committee that did not necessarily meet all the criteria of a primary study were considered secondary studies. Secondary studies are typically not as methodologically rigorous as primary studies, or they might present findings of altered functioning consistent with later development of a diagnosis but without clear predictive value. Many of the secondary studies relied on self-reports of various diagnoses rather than an examination by a health professional or a medical record review.

As self-reports of health outcomes and exposures account for the bulk of the Gulf War and health literature, the committee decided that it would not exclude such studies but rather considered them to be secondary. The committee recognized the potential for misclassification of a health outcome due to inaccurate recall in such studies. As explained later in this chapter, self-reports of exposure information are also subject to recall bias, and thus in studies where participants self-report both their exposures and their health conditions, there is a greater potential for reporting bias as a result of participants over-reporting both pieces of information. Furthermore, the committee recognizes that self-reports may also be influenced by media attention and potential compensation for service-connected conditions, however, none of the studies reviewed by the committee factored these considerations into their evaluations.

Other Related Studies

The Volume 10 committee also considered a number of studies that did not meet the criteria for a primary or secondary study, but nonetheless provided information on the health of Gulf War veterans. Examples of such studies might be those that looked at a health outcome of interest in veterans and its association with another health outcome in veterans, that is, not a comparison between deployed and nondeployed veterans. For example, a study may assess whether cardiovascular conditions in deployed veterans are associated with their alcohol use. Other studies focused on neuroimaging approaches to detect changes in the brains of veterans with Gulf War illness or on the identification of human genotypes that may be markers for the diagnosis or treatment of Gulf War illness. These studies and other relevant studies were also reviewed by an expert on the committee and then discussed by the full committee. In an effort to

be inclusive, these ancillary studies are discussed in a section called "Other Related Studies" for each health outcome to which they pertain; however, no conclusions were based solely on these ancillary studies.

INDIVIDUAL VARIABILITY

Differences among people in their genetic, biologic, psychologic, and social vulnerabilities add to the complexities in determining health outcomes related to specific agents. The likelihood of observing a particular health outcome may differ for people with increased sensitivity to an agent. A person who is a poor metabolizer of a particular substance, depending on his or her genetic makeup, might be at higher or lower risk for specific health effects if exposed to the substance. For example, researchers are investigating butyrylcholinesterase enzyme levels and genotypes in veterans with and without Gulf War illness to try to determine whether a specific enzyme genotype puts a veteran at higher risk of developing the illness if they used PB during the war (Steele et al., 2015).

Another aspect of individual variability can be a residual genetic confounder (Khoury and Yang, 1998), in which an unassessed but potentially measureable genetic factor could be associated with the exposure and outcome of interest; such confounding may have a particularly important role in smaller case-control studies. For example, an exposure to Gulf War deployment found to be associated with an outcome of interest could instead have a genetic residual confounder (not otherwise assessed) explaining the relationship. Genetic risk markers are often differentially represented in various populations, especially across race-ethnicities (and even within seemingly uniform groups), and are thus important to consider in certain diseases, especially those with known causal associations related to highly or fully penetrant genes.

EXPOSURE ASSESSMENT

Chapter 1 and earlier volumes of the *Gulf War and Health* series describe the possible exposures Gulf War military personnel might have experienced. Volume 4 also details the exposure modeling and biological monitoring that was conducted by the Department of Defense (DoD) and others to estimate troop exposures to some chemical agents such as depleted uranium, sarin and cyclosarin, and smoke from oil-well fires. As noted in that chapter, there is poor agreement between subjective and objective measurements of exposures to depleted uranium and oil-well fire smoke. Some studies also show evidence of reporting bias regarding vaccinations and ingestion of pyridostigmine bromide tablets. The modeling of the possible exposures to sarin and cyclosarin from the demolition of the Khamisiyah complex has also been criticized. The committee did consider studies that compared health outcomes seen in deployed veterans who may or may not have been exposed to nerve agents as a result of the Khamisiyah detonation and to oil-well–fire smoke; some of these studies also included nondeployed control groups.

Limitations of Exposure Information

Very little is known about most Gulf War exposures. After the ground war, an environmental-monitoring effort was initiated primarily because of concerns related to smoke from oil-well fires and exposure to sarin and cyclosarin. Monitoring for the other agents to which

the service members might have been exposed was not conducted. Consequently, exposure data (such as the actual agents, the duration of exposure, the route of entry, measures of external exposure (e.g., air concentrations), the internal dose, and documentation of adverse reactions) on those other agents are lacking or severely limited. For example, a DoD-sponsored post-war survey conducted by RAND Corporation assessed possible exposures to pesticides—both those condoned or supplied by the military and those obtained from nonmilitary sources (Fricker et al., 2000). The survey found that the majority of service members used some form of pesticide, in many cases multiple pesticides, and that some troops may have over- or misused pesticides during their deployment.

Various exposure assessment tools have been used in research to fill gaps in exposure information, but there are problems in reconstruction of past exposure events. Many studies have assessed military personnel exposures to various preventive agents including PB and pesticides agents during the Gulf War. These studies have been based on an individual's recall of the agents he or she received or took, frequently in stressful situations. Recall information has rarely been verified by in situ measurements or examination of military records. Furthermore, many of the surveys used to assess potential exposures were conducted several to many years after the war was over (Fricker et al., 2000), such as the National Health Survey of Gulf War Veterans and their Families conducted in 1995 (Kang et al., 2000). For example, veterans have been surveyed to obtain recollections about agents to which they might have been exposed, although survey results might be limited by recall bias and even a lack of familiarity with what the potential exposures were, such as the names of pesticides (Fricker et al., 2000).

Extensive efforts have been made to model and obtain information on potential exposures to DU, smoke from oil-well fires, and other agents. Models have been refined to estimate exposures to sarin and cyclosarin, but it is difficult to incorporate intelligence information, meteorologic data, transport and dispersion data, and troop-unit location information accurately (see Volume 4, Chapter 2, "Exposures in the Persian Gulf"). Although modeling efforts are important for discerning the details of exposures of Gulf War veterans, they require external review and validation. Furthermore, even if there were accurate troop location data, the location of individual service members would be very uncertain. Because of the limitations in the exposure data, it is difficult to determine the likelihood of increased risk for disease or other adverse health effects in Gulf War veterans that are due specifically to biologic and chemical agents.

Multiple Exposures and Interactions

Compounding the difficulty in assessing deployment exposures is the fact that military personnel were potentially exposed to numerous harmful agents simultaneously and sequentially. Many of the exposures were not specific to the Gulf War (e.g., diesel and solvents), although others were (e.g., PB, nerve agents), but the number and combination of agents to which the veterans might have been exposed make it difficult to determine whether any specific agent or combination of agents is the cause of many of the Gulf War veterans' illnesses. As noted by the Volume 6 committee (IOM, 2008b) on deployment-related stress, most the studies that assessed Gulf War exposures queried veterans about a prescribed list of exposures that the investigators thought the veterans might have experienced. Few of the studies asked open-ended questions about what the exposures or conditions were, nor did they ask about the frequency, intensity, or duration of those exposures. Furthermore, although some exposure surveys were conducted

shortly after the conclusion of the war (e.g., Sutker et al., 1993), other surveys were conducted several and even many years after the war (e.g., Proctor et al., 1998), making it difficult to determine the accuracy of the veterans' recall of their exposures during a stressful period and after a substantial lapse of time. The Volume 10 committee also recognizes that at 25 years after the war, continuing to survey veterans about their exposures during the war is unlikely to yield any new exposure information or help to model those exposures.

Addressing multiple exposures has been a subject of much debate and research in the fields of toxicology, environmental and occupational health, and medicine, and although much progress has been made, the interactions of harmful agents in both humans and animals are not well understood. Exposure to multiple agents or stressors may result in interactions among the agents that produce an effect that might not have occurred otherwise, or they might result in a greater effect, or in a different effect than that caused by exposure to one of the agents alone. Thus, attributing an effect to one agent or a combination of agents is difficult, especially in situations involving many different types of exposures (e.g., chemicals, heat, psychological stress, vaccines). The complexity of assessing the effects of multiple exposures and interactions is further compounded by the uncertainty of knowing what exposures a given service member experienced, nor their frequency, intensity (e.g., concentration), or duration.

CATEGORIES OF ASSOCIATION

The committee attempted to express its judgment of the available data clearly and precisely in the "Conclusions" section for each health outcome. It agreed to use the categories of association that have been established and used by previous Gulf War and Health committees and other IOM committees (IOM, 2000, 2003, 2005, 2006b, 2007, 2010). Those categories of association have gained wide acceptance by Congress, government agencies (particularly the Department of Veterans Affairs), researchers, and veterans groups.

The five categories below describe different levels of association and present a common message: the validity of an association is likely to vary to the extent to which common sources of spurious associations could be ruled out as the reason for the observed association. Accordingly, the criteria for each category express a degree of confidence based on the extent to which sources of error were reduced. The committee discussed the evidence and reached consensus on the categorization of the evidence for each health outcome in Chapter 4.

Sufficient Evidence of a Causal Relationship

Evidence is sufficient to conclude that a causal relationship exists between being deployed to the Gulf War and a health outcome. The evidence fulfills the criteria for sufficient evidence of a causal association in which chance, bias, and confounding can be ruled out with reasonable confidence. The association is supported by several of the other considerations used to assess causality: strength of association, dose–response relationship, consistency of association, temporal relationship, specificity of association, and biologic plausibility.

Sufficient Evidence of an Association

Evidence suggests an association, in that a positive association has been observed between deployment to the Gulf War and a health outcome in humans; however, there is some doubt as to the influence of chance, bias, and confounding.

Limited/Suggestive Evidence of an Association

Some evidence of an association between deployment to the Gulf War and a health outcome in humans exists, but this is limited by the presence of substantial doubt regarding chance, bias, and confounding.

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

The available studies are of insufficient quality, validity, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between deployment to the Gulf War and a health outcome in humans.

Limited/Suggestive Evidence of No Association

There are several adequate studies, covering the full range of levels of exposure that humans are known to encounter, that are consistent in not showing an association between deployment to the Gulf War and a health outcome. A conclusion of no association is inevitably limited to the conditions, levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small increase in risk at the levels of exposure studied can never be excluded.

CONCLUSIONS

Complicating the issue of Gulf War veterans' health is the inexorable march of time. Aging itself is associated with an increased prevalence of health conditions even among people who have never been in the military or deployed. The aging of the Gulf War veteran population—now at least 43 years old—makes it difficult in many cases to distinguish health outcomes associated with the Gulf War, such as the joint pain and cognitive deficits that are symptomatic of Gulf War illness, from those that occur normally with increasing age. Furthermore, many diseases that are more common in older adults, such as some cancers, have long latencies of onset that also complicates the identification of a possible cause of the disease be it Gulf War deployment, aging, or some other event. This distinction is important because it is possible that exposure during deployment when the veteran was relatively young may increase the likelihood of later age-related disease. However, the challenge of understanding the effects of aging can be addressed with well-designed epidemiologic studies that select appropriate reference populations and apply rigorous analytical methods.

The epidemiologic and clinical studies conducted to date have provided valuable information regarding the health of Gulf War veterans; however, many of the studies have significant limitations of design or implementation that hinder accurate assessment of the veterans' health status. The limitations include the possibility that study samples do not represent the entire Gulf War population, low rates of participation in studies, narrow assessment of health

status, reinforcement of self-reporting of symptoms and exposures in response to media attention, insensitivity of instruments for detecting abnormalities in deployed veterans, and a period of investigation that is long past the time of exposure. For some studies, particularly those conducted in the decade or so after the war, the period of investigation may have been too brief to detect health conditions that have a long latency or require many years to progress to the point where disability, hospitalization, or death occurs. Many of the U.S. studies are cross-sectional, and this limits the opportunity to learn about symptom duration and chronicity, latency of onset, and prognosis. In addition, the problem of multiple comparisons that is common in many of the Gulf War studies results in confusion over whether the effect is real or occurring by chance. These limitations make it difficult to interpret the results of study findings, particularly when several well-conducted studies produce inconsistent results.

The committee's process for reaching conclusions about the strength of the association between deployment to the Gulf War and its potential for adverse health outcomes was collective, interactive, iterative, and based on the process used by the Volume 8 committee. The committee thoroughly evaluated the scientific literature attending to the design, methodological, and special considerations described above, particularly the limitations of exposure information and outcomes assessment. The evaluation process as implemented by the committee ensured a rigorous review and clear response to the committee's charge.

3

HUMAN COHORT STUDIES AND THEIR DERIVATIVES

This chapter describes the major cohort studies and their derivative studies used by the Volume 10 committee to provide the evidence for the conclusions presented in Chapter 4. It provides an overview of the major cohort studies of Gulf War veterans, and it describes in detail the populations studied, the methods used to select those populations, and the approaches used to identify the health status of the veterans—including questionnaires, clinical examinations, and laboratory tests. Much of this information was previously described in Volumes 4 and 8 (IOM, 2006b, 2010); however, new studies on established cohorts are discussed where available, and the committee has included a description of three additional Gulf War cohorts that were not discussed in the previous volumes. The findings from the studies described in this chapter are evaluated in Chapter 4 where appropriate.

Cohort studies are important for understanding the health of Gulf War veterans. Some of these cohorts were brought together in the first few years after the Gulf War; others were assembled more recently. The largest studies of Gulf War veterans have been conducted in countries that were members of the Gulf War coalition, including the United States, the United Kingdom (UK), Denmark, Canada, and Australia. Most of the studies compare sizable groups of deployed veterans with groups of nondeployed veterans or with veterans who were deployed to locations other than the Persian Gulf region (for example, Bosnia or Germany). The first publication describing these cohorts is referred to as the reference study.

Some cohorts, once established, led to numerous studies, or multiple publications that examined more detailed questions about Gulf War veterans' health; the committee refers to those studies as derivatives. A derivative study[2] is included and summarized under the original cohort (reference study) from which the study population was drawn. This organization helped the committee identify populations that have been studied and understand which studies were independent of one another; establishing which studies rely on the same population sample is important because it helped the committee avoid double counting when weighing the evidence.

The cohort studies of Gulf War veterans and their derivative studies have contributed greatly to the understanding of veterans' health, but they have limitations that are encountered in many epidemiologic studies (see Chapter 2), including lack of representativeness, selection bias, lack of adjustment for potential confounding factors, self-reports of exposures, lack of a diagnosis by a health professional for some health effects, and outcome misclassification.

[2] Derivative studies may simply be publications reporting additional results, subcohort analyses, or nested case-control studies based on the population described by the reference study.

ORGANIZATION OF THIS CHAPTER

For each separately assembled cohort included in this chapter, the reference study is described first, followed by a summary of any derivative studies cited in Chapter 4. Cohorts of U.S. veterans are presented first, followed by population-based cohort studies of British, Australian, Danish, and Canadian veterans. The committee identified only a few new studies published since 2009 for most of the cohorts. The Volume 10 committee included studies on three additional Gulf War veteran cohorts not described in depth in Volumes 4 or 8. However, given that those cohorts have resulted in multiple publications (e.g., Iannacchione et al., 2011) and specifically address concerns identified in the statement of task (e.g., multiple sclerosis and amyotrophic lateral sclerosis), they receive more in-depth consideration in this volume.

Not all derivative studies for a particular cohort study are included in this chapter or in Chapter 4. In many cases, the derivative studies were highly specialized; for example, they reported on family issues, subclinical changes, or treatment outcomes. Table 3-1 at the end of the chapter lists the reference and derivative studies for each cohort cited in Volumes 4 and 8 and in this volume.

U.S. VETERAN COHORTS

Most cohort studies are population-based and drawn from the entire population of veterans (Kang et al., 2000) while others are based on state of residence (Iowa Persian Gulf Study Group, 1997; McCauley et al., 1999a; Steele, 2000), and some are drawn based on military unit or base (Proctor et al., 1998; Haley et al., 1997a; Gray et al., 1999a; Fukuda et al., 1998; Stretch et al., 1995). Additional groups of U.S. veterans have been drawn based on disease (Wallin et al., 2012; Horner et al., 2003).

Department of Veterans Affairs National Health Survey

The Department of Veterans Affairs (VA) is conducting a longitudinal survey of 30,000 veterans known as the National Health Survey of Gulf War Veterans and Their Families (NHS). Thus far, three survey waves have been conducted: wave 1 in 1993–1995 (Kang et al., 2000) with physical examinations in 1999–2001 (Eisen et al., 2005), wave 2 in 2003–2005 (Kang et al., 2009), and wave 3 in 2012–2013 (Bossarte, 2014; Dursa et al., 2016). Volume 4 described seven derivative studies of the NHS, and Volume 8 identified six additional derivative studies of this cohort that examine specific health outcomes or conducted a follow-up survey and analysis. Since 2009, four new studies have been published based on the second wave survey. Preliminary results from wave 3 were presented to the committee by a VA representative (Bossarte, 2014) and some of the results have been recently published (Dursa et al., 2016).

Reference Study

A major population-based study of U.S. veterans was mandated by Public Law 103-446 in 1994 to estimate the prevalence of symptoms and other health outcomes (including reproductive outcomes in spouses and birth defects in children) in Gulf War deployed versus nondeployed veterans. This retrospective study was designed to be representative of the nearly 700,000 U.S. veterans sent to the Persian Gulf and 800,680 veterans who were not deployed but who were in the military between September 1990 and May 1991.

For wave 1 of the NHS, VA mailed questionnaires to a stratified random sample of 15,000 deployed and 15,000 nondeployed Gulf War veterans identified by the Defense Manpower Data Center (DMDC) (Kang et al., 2000). Women and those serving in the National Guard and reserves were oversampled, resulting in a study population that was approximately 20% women, 25% National Guard, and 33% reservists. The controls were stratified by gender, unit component, and branch of service to mirror the population of deployed veterans. The self-administered structured health questionnaire contained a 48-symptom inventory (somatic and psychological symptoms) and questions about chronic medical conditions, functional limitations, use of medical services, and environmental exposures (e.g., immunizations, use of the prophylactic antinerve agent pyridostigmine bromide [PB], smoke from oil-well fires, and pesticides and insecticides).

Wave 1 also used telephone interview software in an attempt to capture those who did not respond to the mailed questionnaire. A total of 11,441 (75%) deployed and 9,476 (64%) nondeployed veterans participated in the study; 15,817 veterans responded to the questionnaire, and 5,100 responded to the telephone interview (Kang et al., 2000; Kang and Bullman, 2001). In addition, medical records were obtained for a random sample of 4,200 respondents to validate self-reports of clinic visits or hospitalizations within the last year. Of the 2,233 veterans with at least one clinic visit, 43.2% provided medical record release consent; of the 310 with at least one hospitalization, 45.2% provided medical record release consent. Medical record reviews verified more than 90% of self-reported reasons for clinic visits or hospitalizations (Kang et al., 2000).

Kang et al. (2000) did not assess exposure–symptom relationships but rather noted the percentage of veterans who reported each of 23 environmental exposures and nine vaccine or prophylactic exposures (such as to PB). The five most common environmental exposures reported by more than 60% of survey participants were diesel, kerosene, or other petrochemical fumes; local food other than that provided by the armed forces; chemical protective gear; smoke from oil-well fires; and burning trash or feces.

Derivative Studies

In Volume 4, seven derivative studies of the NHS were identified: Davis et al. (2004), Eisen et al. (2005), Kang et al. (2001, 2002, 2003, 2005), and Karlinsky et al. (2004).

Davis et al. (2004) studied the presence of distal symmetric polyneuropathy determined by medical history, physical examination by a neurologist, blood tests, and standardized electrophysiologic assessment of motor and sensory nerves in a cohort subset of 1,061 deployed veterans and 1,128 nondeployed veterans from wave 1 of the NHS. Spouses of deployed (n = 484) and nondeployed (n = 533) veterans were studied to evaluate whether an infectious agent or environmental contaminant brought back from the gulf could be responsible for any adverse health outcomes. Evaluations of 244 Khamisiyah-exposed (data provided by the Department of Defense [DoD]) versus 817 nonexposed deployed veterans for the presence of distal symmetric polyneuropathy were conducted.

In 1999–2001, Eisen and colleagues (2005) performed a cross-sectional study on numerous health outcomes of Gulf War veterans who had participated in wave 1 of the NHS. The study population consisted of a stratified random sample of the 11,441 deployed and 9,476 nondeployed veterans who had responded to the mailed questionnaire or telephone interview described above. This study included a comprehensive medical examination and laboratory testing. Of the 1,996 eligible deployed veterans, 1,061 (53.1%) were examined; 680 (34.1%) declined and 255 (12.8%) were not located. Of the 2,883 eligible nondeployed veterans, 1,128

(39.1%) were examined; 1,316 (45.7%) declined and 439 (15.2%) were not located. Despite extensive recruitment efforts, the participation rate for this study was low—60.9% of deployed veterans and 46.2% of the nondeployed.

Study participants were assigned a medical center closest to their residence where physicians and nurses performed medical, neurologic, psychiatric, and gynecologic histories and examinations; laboratory, nerve conduction, pulmonary function, and neuropsychological tests were also performed. Twelve primary health outcome measures and physical functioning were examined using the SF-36.[3] Outcome measures were chosen by the authors to cover the most common symptoms reported by veterans, such as musculoskeletal pain, fatigue, rashes, and neuropathy (Kang et al., 2000).

Kang and colleagues (2001) assessed the association between self-reported adverse pregnancy outcomes and deployment to the gulf using data from the wave 1 questionnaire. Results are based on the 3,397 (2,761 males, 636 females) deployed and 2,645 (1,951 males, 695 females) nondeployed veterans who reported their or their partner's first pregnancy ending after June 30, 1991.

A nested case-control analysis was performed on the 277 (2.4%) deployed veterans from wave 1 who met the case definition for a possible neurological cluster of symptoms including blurred vision, loss of balance or dizziness, tremors or shaking, speech difficulty, concentration or memory problems, and irregular heartbeat, to determine which of 23 self-reported exposures were more common among cases than among the controls (6,730 Gulf War veteran respondents who lacked symptoms) (Kang et al., 2002). Exposure to a variety of chemical agents were reported to be higher among cases than controls, specifically to chemical-agent-resistant compound paint, depleted uranium, nerve gas, food contaminated with oil or smoke, and bathing in or drinking water contaminated with oil or smoke.

Kang et al. (2003) used the wave 1 participants to assess the prevalence of posttraumatic stress disorder (PTSD) and chronic fatigue syndrome (CFS) in Gulf War veterans. The questionnaire administered to the veterans in 1993–1995 had included eight symptoms to be used to diagnose CFS, and the PTSD Checklist was used to identify symptoms of PTSD. Assessment of CFS was based on the Centers for Diseases Control and Prevention (CDC) case definition after exclusion of alternate medical causes of the symptoms.

Kang and colleagues (2005) conducted a nested case-control study evaluating the role of sexual assault on the risk of PTSD from the 11,441 Gulf War veteran respondents of the 1995 questionnaire described above. A score of 50 or higher on the PTSD Checklist was necessary to have met the criteria for PTSD; 1,381 (12.1%) Gulf War veterans (336 females and 1,045 males) screened positive for PTSD, while 10,060 (1,795 females and 8,265 males) screened negative and were used as a comparison group. Adjustments for age, race, branch, combat, rank, and unit component, and self-report of sexual harassment and assault were made.

Karlinsky and colleagues (2004) examined pulmonary function and self-reported respiratory symptoms in 1,036 deployed and 1,103 nondeployed veterans who completed the clinical examination component of the NHS. Results of pulmonary function tests were classified into five categories: normal pulmonary function, nonreversible airway obstruction, reversible airway obstruction, restrictive lung physiology, and small-airway obstruction. The authors also reported on the pattern of pulmonary function test results in those exposed (n = 159) and those

[3] The Medical Outcome Study's 36-item questionnaire, known as the Short Form-36 or SF-36, is a standardized instrument to measure physical and mental health, physical and social functioning, and general well-being.

not exposed (n = 877) (according to DoD exposure estimates developed in 2002) to nerve agents from destruction of munitions at the storage site at Khamisiyah in 1991.

The Volume 8 committee identified six studies of the NHS cohort (Blanchard et al., 2005; Kang et al., 2009; Page et al., 2005a,b; Toomey et al., 2007, 2009) published after Volume 4. The committee notes that VA uses the term chronic multisymptom illness rather than Gulf War illness and thus the discussions of the NHS cohort below use the former term.

Page and colleagues (2005a) assessed the possible health effects of Khamisiyah exposure (determined from models developed by the DoD and Central Intelligence Agency) in 5,555 Army veterans drawn from the cohort of 11,441 deployed veterans who responded to the wave 1 questionnaire. When the survey was completed in 1995, veterans were not yet notified of possible chemical agent exposure in Khamisiyah. Comparisons were made between the 1,898 exposed and 3,336 unexposed veterans.

Page and colleagues (2005b) also examined the association between notification of possible exposure at Khamisiyah and self-reported morbidity. In 2000, a subsample of 1,056 deployed Army veterans was surveyed; of the 600 notified subjects, 438 (73%) responded, and of the 456 nonnotified subjects, 318 (70%) responded.

Blanchard and colleagues (2005) assessed the prevalence and severity of chronic multisymptom illness (CMI) in the same cohort of 1,061 deployed and 1,128 nondeployed veterans as described by Eisen and colleagues (2005). Combat exposure was significantly associated with CMI. The prevalence of CMI in the nondeployed population remained relatively constant at 4, 7, and 10 years postwar. Among the deployed veterans, CMI prevalence decreased from 44.7% at 4 years to 28.9% after 10 years (Fukuda et al., 1998; Steele, 2000). Blanchard et al. (2005) also assessed for the presence of CMI based on the possible exposure of deployed veterans to nerve agents as a result of the Khamisiyah demolition. Based on DoD modeling, 236 (22.2%) of the deployed veterans were exposed; 92 (39.0%) had CMI and 144 (61.0%) did not.

Toomey and colleagues (2007) examined the prevalence of mental health disorders, self-report of symptoms, and quality of life 10 years postconflict in the same cohort of 1,061 Gulf War deployed and 1,128 nondeployed veterans as that of Eisen et al. (2005). Neuropsychological functioning was also evaluated in the same population (Toomey et al., 2009). The measures (e.g., general intelligence, attention or executive functioning, motor ability, visuospatial processing, and verbal and visual memory) were based on those previously found to be different between the same deployed and nondeployed groups as in earlier studies.

Kang and colleagues (2009) conducted a 10-year follow-up general health assessment of Gulf War veterans in wave 2 of the NHS. For this wave, VA and Social Security records through December 2002 were used to identify and mail health questionnaires to the 29,607 living veterans who had been sampled in wave 1 (15,000 Gulf War deployed and 15,000 nondeployed). Telephone interviews were conducted with 2,000 nonresponsive participants and a sample of 1,000 participants who had indicated a clinic visit or hospitalization within the previous 12 months in order to obtain permission for medical record retrieval. As a result of those recruitment efforts, 6,111 (40%) deployed and 3,859 (27%) nondeployed participants responded to the survey; the overall response rate was low, only 34%. The administered questionnaire was a modified version of that used in the 1995 survey and included the PTSD Checklist, the Patient

Health Questionnaire, and the SF-12[4] in addition to other items used to assess general health status.

The Volume 10 committee identified five new published studies that met its inclusion criteria, which were all based on data from the second wave of the NHS (Wallin et al., 2009; Li et al., 2011a, 2014; Coughlin et al., 2011a,b). A fifth study describing preliminary results of the third wave of the NHS was presented to the committee by a VA representative (Bossarte, 2014; Dursa et al., 2016).

In 2003–2004, Wallin et al. (2009) assessed neuropsychologic performance in Gulf War deployed veterans with Gulf War illness (n = 25) and without (n = 16) who were recruited from the first wave of the NHS and who lived in the mid-Atlantic region (248 veterans were contacted). Cases were defined based on the CDC criteria for Gulf War illness. Participants completed an interview and full day of cognitive testing. The neuropsychological testing battery included assessment of verbal abilities, attention, memory and learning, problem solving, and motor skills. Other assessments included the Personality Assessment Inventory and SF-36. Additional data was extracted from responses to the first wave of the NHS. Regression analyses were adjusted for demographic and military variables.

In an assessment of 8,822 veterans who completed both the 1995 and 2005 surveys, Li et al. (2011a) reported changes in health and chronic diseases. Baseline data from the 1995 survey and follow-up data from the 2005 survey were used to assess longitudinal change for each individual. Weights for gender, service branch, and unit component were applied to estimate population prevalence rates.

Using data from the second wave of the NHS in 2003–2005, Coughlin et al. (2011b) assessed the association between alcohol consumption in 9,970 respondents and unexplained multisymptom illness (defined as having unexplained physical symptoms and illnesses that persisted for 6 months or longer and were not explained by other diagnoses) while adjusting for age, sex, race/ethnicity, branch of service, rank, and deployment status. The authors used the same survey results to assess the association between body weight and various health conditions (Coughlin et al., 2011a).

In a small case-control study conducted by Li et al. (2014), among the respondents of the 2005 survey, Li et al. sampled 200 Gulf War veterans with "chronic fatigue-like multi symptoms" and 398 controls veterans. From those contacted, 16 Gulf War veterans and 12 control veterans completed a telephone interview, met eligibility criteria, and completed a clinical exam with autonomic testing (conventional large fiber nerve conduction, quantitative sensory testing, baseline autonomic testing, quantitative sudomotor axon reflex test, and diagnostic tilt-table test).

During an open session, VA made a presentation to the Volume 10 committee on the most recent results of the third survey wave of the NHS (Bossarte, 2014). Results from this survey were not published until early 2016 (Dursa et al., 2016). This survey consisted of the same 30,000 Gulf War deployed and era veterans and the same administration methods as the two prior surveys, that is via mail, website, or a computer-assisted telephone interview. A total of 14,252 veterans responded (8,104 deployed and 6,148 era veterans), for a response rate of 50%

[4] "The 12-Item Short Form Health Survey (SF-12) was developed for the Medical Outcomes Study, a multiyear study of patients with chronic conditions. The instrument was designed to reduce respondent burden while achieving minimum standards of precision for purposes of group comparisons involving multiple health dimensions" (RAND Corporation, 2010).

(57% deployed, 43% nondeployed). Respondents were more likely to have served in the Army compared with other branches, been deployed, been an officer, be older, and to identify as white than were nonrespondents (Dursa et al., 2016). In a follow-up email to the committee, VA stated that 7,399 veterans participated in both the 2005 and 2013 surveys (Personal communication, Robert Bossarte, VA, January 26, 2015).

The wave 3 questionnaire was modified from the earlier versions, but it again collected information about the presence of various symptoms such as fatigue, muscle or joint pain, headaches, memory problems, and respiratory problems; functional status; activity limitations; health perceptions; chronic medical conditions (self-report of provider diagnoses); mental health disorders; health care utilization; medications; women's health; and potential confounders such as the use of alcohol and cigarettes. No questions on environmental exposures were included. The questionnaire contained modules of validated self-report assessments including the PTSD Checklist-Civilian version. Groups of symptoms were used to identify the presence of CMI (Bossarte, 2014).

A sample of 2,500 veterans who had completed the questionnaire and who had provided a valid response to either "reason for clinic or doctor visit in the past 12 months" or "reason for hospitalization within past 12 months" were selected for medical record validation. In the medical record review subset, 86% of self-report responses for reasons for clinic visit or hospitalization were verified by medical records (Bossarte, 2014). Weighted prevalence estimates and adjusted odds ratios (models were adjusted for age, sex, race, body mass index, smoking status, service branch, and unit component) were presented for several self-reported medical conditions among deployed and nondeployed veterans (Dursa et al., 2016).

Although the data in the presentation by Bossarte (2014) were unpublished and not peer reviewed during the course of the committee's deliberations, they are included in Chapter 4 when data were not included in the Dursa et al. (2016) publication because these surveys are among the few sources of data on many health conditions in a large group of U.S. Gulf War veterans. The Dursa et al. (2016) publication includes additional information about the survey and the statistical methods and weights used in the analysis. It is cited in the discussion of health conditions in Chapter 4 where appropriate.

The Iowa Study

In Volume 4, the Iowa Persian Gulf Study was presented as a reference study with eight derivative studies, and the Volume 8 committee identified three studies derived from the original Iowa cohort. No new studies using this cohort were identified by the Volume 10 committee.

Reference Study

The Iowa study was a cross-sectional survey of a representative sample of 4,886 military personnel who listed Iowa as their home of record at the time of enlistment and served between August 2, 1990, and July 31, 1991 (Iowa Persian Gulf Study Group, 1997). The DMDC identified a representative sample of 28,968 potentially eligible military personnel.

Study subjects were divided into four groups: Gulf War-deployed active duty, Gulf War-deployed National Guard or reserve, Gulf War nondeployed active duty, and Gulf War nondeployed National Guard or reserve. Random samples were evenly selected from each of the four groups for a total of 4,886 study subjects. Of the study subjects who were contacted, 3,695 (76%) completed a telephone interview. Trained examiners used standardized questionnaires,

instruments, and scales from the following to collect information: National Health Interview Survey; Behavioral Risk Factor Surveillance Survey; National Medical Expenditures Survey; Primary Care Evaluation of Mental Disorders; Brief Symptom Inventory; CAGE questionnaire (for alcoholism)[5]; PTSD Checklist—Military; CDC Chronic Fatigue Syndrome Questionnaire; Chalder Fatigue Scale; American Thoracic Society questionnaire; and the Sickness Impact Profile.

No clinical examinations were performed; rather, before conducting their telephone survey, researchers grouped sets of symptoms from their symptom checklists into a priori categories of diseases or disorders. After a veteran identified himself or herself as having the requisite set of symptoms, researchers analyzing the responses considered the veteran as having symptoms "suggestive" of or consistent with a particular disorder but not as having a formal diagnosis of the disorder.

Gulf War veterans scored significantly lower on all eight subscales for physical and mental health on the SF-36. The subscales for bodily pain, general health, and vitality showed the greatest absolute differences between deployed and nondeployed veterans. The Iowa study assessed exposure–symptom relationships by asking veterans to report on their deployment exposures including to solvents or petrochemicals, smoke or combustion products, lead from fuels, pesticides, ionizing or nonionizing radiation, chemical warfare agents, PB use, infectious agents, and physical trauma (Iowa Persian Gulf Study Group, 1997).

Derivative Studies

Eight derivative studies of the Iowa cohort were described in Volume 4 (Black et al., 1999, 2000, 2004a,b; Doebbling et al., 2000; Zwerling et al., 2000; Barrett et al., 2002; Lange et al., 2002). The Volume 8 committee identified three new studies of this cohort.

Subsequent cross-sectional studies of the Iowa cohort examined the presence of possible multiple chemical sensitivity (MCS) in these veterans, including the impact of MCS on quality of life and utilization of health services (Black et al., 1999) and the prevalence of and risk factors for the development of MCS (Black et al., 2000). Self-reports of postwar injuries were also assessed (Zwerling et al., 2000).

Doebbling et al. (2000) used factor analysis to attempt to determine if the symptoms reported by Gulf War veterans after their deployment were different than those reported by nondeployed veterans and if the symptoms seen in the deployed veterans could possibly constitute a unique Gulf War syndrome.

Three studies assessed the prevalence of psychiatric disorders in Gulf War deployed and nondeployed veterans. Barrett et al. (2002) examined the association between PTSD and self-reported physical health status. The prevalence of and risk factors for current anxiety disorder was studied by Black et al. (2004b), who used the PRIME-MD in a structured telephone interview to identify symptoms of anxiety. In a case-control study, however, Black et al. (2004a) used the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (SCID-IV) to diagnose current or lifetime depression in 608 of the Iowa veterans, of whom 192 met the case definition for lifetime depressive disorder (132 deployed and 60 nondeployed). The prevalence of comorbid psychiatric diagnoses was determined.

[5] The CAGE is a four-item scale to assess cutting down (C), feeling annoyed by people criticizing your drinking (A), feeling guilty about drinking (G), and using alcohol as an eye-opener in the morning (E).

Lange et al. (2002) examined the impact of exposure of Gulf War veterans to Kuwaiti oil-well fires and the prevalence of asthma and bronchitis 5 years after the war. Modeled exposures were developed using a geographic information system to integrate spatial and temporal records of smoke concentrations with troop movements ascertained from global positioning system records. Results for modeled exposures were compared with self-reported exposures.

The Volume 8 committee identified three new studies based on the Iowa cohort: Ang et al. (2006) and Forman-Hoffman et al. (2007) both looked at the presence of chronic widespread pain (CWP), and Black et al. (2006) assessed the prevalence of borderline personality disorder.

Approximately 5 years after the initial survey, Ang and colleagues (2006) designed a follow-up evaluation to determine predictive factors for development of CWP in Gulf War veterans. Of the 3,695 veterans in the baseline study, a sample of 602 veterans who previously met the criteria for cognitive dysfunction, depression, or CWP, and a sample of veterans without these problems were evaluated at follow-up.

Forman-Hoffman et al. (2007) also conducted a cross-sectional survey 5 years postconflict to determine the effect of deployment on the development of CWP in the Iowa cohort. The authors used the same 3,695 participants as sampled in Black et al. (2006) below.

Black and colleagues (2006) assessed the prevalence of borderline personality disorder traits in a sample of the Iowa Persian Gulf War veterans using the Schedule for Adaptive and Nonadaptive Personality. The population was drawn from the initial 3,695 surveyed individuals; a second assessment (in-person interviews and medical examinations) was administered to 602 veterans who previously met the criteria for one or more of the following: depression, CWP, and cognitive dysfunction. The overall response rate was 95.7% (n = 576).

Oregon and Washington Veteran Studies

One reference study discussed in Volume 4 examined Gulf War veterans who listed Oregon or Washington as their residence at the time of their deployment (McCauley et al., 1999a); two derivative studies were also described in that volume (Bourdette et al., 2001; Spencer et al., 2001). Neither the Volume 8 nor the Volume 10 committees identified any new studies that used this data set.

Reference Study

Investigators from the Portland Environmental Hazards Research Center examined numerous health outcomes in Gulf War veterans who were deployed between August 1, 1990, and July 31, 1991, and who listed Oregon or Washington as their home state of record at the time of deployment; data was obtained from the DMDC (McCauley et al., 1999a). Beginning in November 1995 and ending in June 1998, a mailed questionnaire was distributed to a representative and random sample (n = 2,343) of the eligible 8,603 Gulf War veterans to assess general health through symptom self-reports; the response rate was 48.4%. The study did not include a nondeployed comparison group. The next phase consisted of a clinical examination of the first 225 participants who showed differences between the symptoms they reported on questionnaires and the symptoms they reported at time of clinical examination.

Derivative Studies

In Volume 4, Bourdette et al. (2001) was considered a reference study although it used the same data set as McCauley et al. (1999a). Bourdette and colleagues (2001) compared 244

potential cases of unexplained illness based on clinical examination and the author's definition of unexplained illness with 113 potential controls that did not meet the case definition from 799 of those eligible for the clinical study, and located participants who had completed the questionnaire described above.

A nested case-control analysis of the cohort examined 142 items related to Gulf War self-reported exposure that might account for cases of unexplained illness (Spencer et al., 2001). The sample consisted of 241 veterans with unexplained illness and 113 healthy controls (drawn from those who completed the 1995–1998 questionnaire above). Multivariate analyses were used to assess associations between Gulf War exposures and unexplained illness. One strength of this study was its elimination of numerous self-reported exposures (such as anthrax and botulinum toxoid vaccines) with questionable validity as determined by lack of test-retest reliability or time-dependent information (for example, chemical weapon exposure reported by precombat veterans or postcombat veterans who could not have been so exposed) (McCauley et al., 1999b).

Kansas Veteran Study

In Volume 4, the study of Kansas Gulf War veterans (Steele, 2000) was considered to be a secondary study for most health outcomes. No derivative studies using the Kansas cohort were identified in that volume, or by the Volume 8 committee. However, since 2009, two nested case-control studies using the Kansas veterans cohort have been published (Steele et al., 2012, 2015).

Reference Study

Using lists of eligible veterans from the DMDC, Steele (2000) conducted a population-based survey to determine health problems of veterans who listed Kansas as their home state of record. A stratified random sample of 3,138 veterans was selected; 2,396 (76%) were located with in-state contact information, of whom 2,211 met further eligibility requirements. Of those, 2,030 agreed to be interviewed; the response rate was 92%. The sample included 1,548 deployed veterans and 482 nondeployed veterans.

The survey, mailed out in 1998, inquired about 16 specific physician-diagnosed or physician-treated medical or psychiatric conditions; 37 symptoms; service branch and locations during the Gulf War (including whether the veterans were notified about the Khamisiyah demolitions); and vaccinations. Using her own definition of Gulf War illness (see the Chapter 4 section on Gulf War illness for the definition), which was similar to that used by CDC (Fukuda et al., 1998), Steele assessed the prevalence of Gulf War illness and associations with Gulf War deployment.

Derivative Studies

Steele et al. (2012) conducted a case-control study in 2000 that compared Gulf War veteran's exposures in a population-based sample of 304 deployed veterans residing in the greater Kansas City metropolitan area, 144 with Gulf War illness and 160 healthy controls out of 906 households contacted (86% response rate, 68% participation rate). Gulf War illness case status was determined based on screening using the CDC definition and subsequent inclusion in the study based on the Kansas definition for Gulf War illness. Potential participants were excluded if they reported being diagnosed with a chronic health condition that could explain their symptoms (e.g., diabetes or lupus), had persistent problems due to chronic infection or injury, reported diagnoses of schizophrenia or bipolar disease, or were hospitalized for alcohol or drug dependence, depression, or PTSD. At the study location, participants completed self-

administered questionnaires about their deployment locations and duration and whether they had any of 19 specific exposures or experiences during deployment, and provided blood samples for another study on genetic factors and enzyme activity.

The blood samples were used to assess the relationship between butyrylcholinesterase genotype and Gulf War illness (Steele et al., 2015). All 304 participants were included in this second study. Genotype and butyrylcholinesterase enzyme activity for Gulf War illness cases were compared with healthy controls. Post hoc analyses examined effects of confounding factors and interaction between multiple factors, including reported exposures.

Fort Devens and New Orleans Cohort Studies

Gulf War veterans from military units stationed in Fort Devens, Massachusetts, and in New Orleans are among the most studied groups of U.S. Gulf War veterans. The reference study (Proctor et al., 1998) and three derivative studies (White et al., 2001; Proctor et al., 2001a,b) from the cohort were described in Volume 4. The Volume 8 committee identified one additional study (Proctor et al., 2006), but the Volume 10 committee did not identify any new studies of these veterans.

Reference Study

The symptom experience of two deployed cohorts of Gulf War veterans was studied by Boston-based researchers. The first, an Army cohort based in Fort Devens, Massachusetts, was surveyed longitudinally. From 1994 to 1996, Proctor et al. (1998) surveyed the deployed cohorts (Fort Devens and New Orleans) with a medical and occupational history questionnaire, an environmental interview, a battery of neuropsychological tests, and scales assessing psychological symptoms. Psychological symptoms were assessed with the Brief Symptom Interview and the Mississippi Scale for PTSD; psychiatric disorders were diagnosed using the Clinician Administered PTSD Scale and the Structured Clinical Interview for DSM-IIIR Axis I Disorders, and structured interviews assessing psychological outcomes. A second deployed cohort from New Orleans and a unit deployed to Germany during the Gulf War were studied only at the second time period. The unit deployed to Germany, serving as controls (n = 47), was an air ambulance company of National Guard from Maine that handled wounded personnel evacuated from the gulf. The study's nearly 300 subjects were a stratified random sample of 2,949 troops (n = 220) from Fort Devens and 928 (n = 73) from New Orleans; both groups consisted of active duty, reserve, and National Guard troops.

Derivative Studies

Psychiatric interviews and other clinical evaluations were administered between 1993 and 1994 to all three cohorts. White et al. (2001) assessed neuropsychological functioning in the cohorts and examined whether any links could be made between performance on a battery of tests and self-reported exposure to a variety of toxicants experienced during deployment. The neuropsychological test battery was designed to assess abilities across the following functional domains: general intelligence, attention/executive function, motor ability, visuospatial processing, verbal and visual memory, mood, and motivation. In addition, eight exposures were surveyed, and respondents were asked to rate each on a scale of 0–2, (0 = no exposure; 1 = exposed; 2 = exposed and felt sick at the time). The authors used standardized regression to identify associations between musculoskeletal, neurologic, neuropsychologic, and psychologic symptoms and several exposures—debris from Scuds and chemical and biologic warfare agents.

The health-related quality of life among the Fort Devens cohort (n = 141) and the Germany deployed cohort (n = 46) was evaluated by Proctor et al. (2001a). The SF-36 was administered to a stratified, random sample of the original cohort approximately 4 years after the war. Proctor et al. (2001b) assessed 180 deployed veterans from the Fort Devens cohort and 46 Germany deployed veterans for symptoms of chronic fatigue and chemical sensitivity to assess the prevalence of the symptoms and whether there was an overlap between these symptoms and the CDC case definition of CMI.

The Volume 8 committee identified one new derivative study. Proctor et al. (2006) assessed neurobehavioral functioning in relationship to potential exposure to sarin and cyclosarin as a result of the demolition of the Khamisiyah munitions dump. Data had been collected in 1994 to 1996, before veterans had been notified about their potential exposure to the nerve agents. The neurobehavioral tests included those for attention, executive function, psychomotor function, visuospatial abilities, and short-term memory.

Seabee Studies

Numerous studies have been conducted on the Seabees, members of the U.S. Naval Construction Force battalions. Two reference studies were included in Volume 4. Haley et al. (1997b) began a study of one cohort of Seabees, and Gray et al. (1999a) surveyed a subset of the Haley cohort that excluded Gulf War veterans who were no longer in the service at the time of their study. Three derivative studies for Haley et al. (1997b) were presented in Volume 4 along with two derivative studies for Gray et al. (1999a). The Volume 8 committee identified five additional derivative studies of the Haley et al. (1997b) cohort, and the Volume 10 committee identified eight additional derivative studies. However, neither the Volume 8 nor the Volume 10 committee identified any derivative studies of the Gray et al. (1999a) cohort.

Haley et al. Studies

Reference Study

In 1994, Haley et al. (1997b) recruited members of the Twenty-Fourth Naval Reserve Construction Force Battalion into an epidemiologic study in an effort to identify syndromes that might help define the variety of symptoms experienced by Gulf War veterans. Study participants were selected from the 606 reserve Seabees living in five southern states who had been called to active duty for the Gulf War. The researchers were able to directly contact 350 of the 429 Seabees for whom the investigators had presumptive addresses from the official in-theater battalion roster; efforts to reach the other 250 Seabees were made by battalion commanders, media coverage, and networking by veterans. Of the 606 Seabees, 41.1% (n = 249) agreed to participate in the study (42% were still on active duty and the rest of the participants had retired); there was no comparison group of nondeployed veterans. A majority of participants (70%) reported having had a serious health problem since returning from the Gulf War. A telephone survey of a random sample of nonparticipants found that, while they were demographically similar to participants, only 43% reported having had serious health problems since the war. Eleven percent of participants and 3% of nonparticipants were unemployed. Of those who participated, more than half (58%) had left the military by the time of the study.

Study participants completed a standardized survey measuring the anatomical distributions or characteristics of each symptom and wartime exposures, and a standard psychological personality assessment inventory. Two-stage factor analysis was used to derive

syndromes from the survey responses. Six syndrome factors were identified based on results from 63 of the 249 Seabee veterans.

- Syndrome 1—impaired cognition—was characterized by symptoms indicative of problems with attention, memory, reasoning, insomnia, depression, daytime sleepiness, and headaches.
- Syndrome 2—confusion-ataxia—was characterized by problems with thinking, disorientation, balance disturbances, vertigo, and impotence.
- Syndrome 3—arthromyoneuropathy—was characterized by joint and muscle pains, muscle fatigue, difficulty lifting, and extremity paresthesias.

The three other syndromes—syndrome 4 phobia-apraxia; syndrome 5 fever-adenopathy; and syndrome 6 weakness-incontinence—demonstrated weaker clustering and overlapped to some extent with syndromes 1 through 3 (Haley et al., 1997b). In most of the derivative studies discussed below, only veterans with syndromes 1 through 3 were assessed.

Derivative Studies

The three syndromes identified by Haley and colleagues (1997b) were the focus of a case-control study that examined the relationship of the syndromes to self-reported exposures to neurotoxicants. The study tested the hypothesis that exposure to organophosphates and related chemicals that inhibit cholinesterase are responsible for the three nervous system-based syndromes (Haley and Kurt, 1997).

Another study by Haley and collaborators (1999) examined whether genetic susceptibility could play a role in placing some veterans at risk for neurologic damage by organophosphate chemicals. The investigators studied 45 veterans: 25 with chronic neurologic symptoms identified through their earlier factor analysis study and 20 healthy controls from the same battalion. Investigators measured blood butyrylcholinesterase and two types, or allozymes, of the enzyme paraoxonase/arylesterase-1. The genotypes encoding the allozymes were also studied.

The Volume 8 committee identified one study by Haley et al. (2009), conducted in 1997–1998, that looked at abnormal brain response to cholinergic challenge in a small group of Gulf War veterans. Twenty-one Gulf War veterans with symptom complexes used by Haley to define three Gulf War illness syndromes and 17 age-, sex- and education-matched controls, underwent a 99mTc-HMPAO-SPECT brain scan with and without an infusion of PB. The Volume 8 committee also summarized other studies by Haley and colleagues on neurologic outcomes as follows:

> Haley and colleagues performed detailed neurologic assessments in several case-control studies of the original cohort of Seabee reservists. The cases were veterans who had met criteria for factor-derived syndromes. Under the hypothesis that those veterans were ill from neurotoxic exposures, especially to organophosphates, the assessments covered broad neurologic function (Haley and Kurt, 1997), autonomic function (Haley et al., 2004), vestibular function (Roland et al., 2000), basal ganglia injury (Haley et al., 2000a,b), normalized regional cerebral blood flow (Haley et al., 2009); and paraoxonase genotype and serum concentrations (Haley et al., 1999).

The Volume 10 committee identified many derivative studies of the Seabee cohort initially described by Haley et al. (1997b). In general, these studies were further assessments of specific aspects of Haley's factor-analysis defined syndromes of Gulf War illness, with an

emphasis on brain structure and function and neurologic endpoints, particularly the neural and cognitive effects of exposure to cholinesterase inhibitors. Many of the derivative studies of the original 249 Seabees fail to provide adequate description of the methods used such as how their subjects were selected or when they were assessed. Because of the small number of veterans that were assessed in the majority of the studies by Haley and colleagues, and because the focus of Volume 8 was not on linking Gulf War exposures to health outcomes, these studies were not discussed in detail in the previous volumes. The Volume 10 committee summarizes the goals of the studies here briefly and discusses them in Chapter 4 in the section on Gulf War illness.

Between June 2008 and July 2009, 48 members of the Seabee cohort attended a week-long clinical, neuroimaging, and neuropsychologic and psychiatric sessions at the University of Texas Southwestern Medical Center in Dallas. Tests included face-name associative memory and face recognition tests, the SCID-IV, and the Clinician-Administered PTSD Scale. Participants also underwent a blinded hippocampus perfusion study in two sessions separated by 2 days, one session with a saline infusion and the second with physostigmine infusion (Li et al., 2011b). The testing goals and protocols are summarized briefly below and results, where relevant, are presented in Chapter 4.

Two studies used magnetic resonance imaging (MRI) to determine blood flow in the brain of veterans with and without Gulf War illness. Li et al. (2011b) used arterial spin labeling perfusion MRI with a physostigmine challenge to compare hippocampal blood flow in a group of veterans with one of three Gulf War illness syndromes (11 veterans with syndrome 1, 13 veterans with syndrome 2, and 11 veterans with syndrome 3) and a control group of 13 well veterans, 11 years after initial testing and 20 years after the war. For this study, 34 Seabees from the 1998 cohort and 23 new Gulf War veterans from the original epidemiologic study (assumed by the Volume 10 committee to be from the 1994 Haley cohort although this was not explicitly stated) were evaluated. Initial testing was conducted with computed tomography. Liu et al. (2011) reported a similar study with a small number of veterans who met Haley's definition for Gulf War illness syndromes 1, 2, and 3 (n = 11, 12, and 10, respectively) and 14 veterans without Gulf War illness. The authors found that using arterial spin labeling with a physostigmine challenge was a cost-effective method for characterizing Gulf War illness syndromes. It was unclear to the committee whether the Li et al. (2011b) and Liu et al. (2011) studies were conducted on the same group of veterans.

In the same population of veterans with and without Gulf War illness as reported by Li et al. (2011b), Odegard et al. (2013) used functional MRI to measure activation of the hippocampus while participants memorized information. The veterans then underwent a face-name associative recall test developed by the authors to assess recall of faces' names as well as intermediate memory states. In yet another study in the same group of Seabees, Moffett et al. (2015) compared measures of complex language (verbal fluency, word generation) and functional magnetic resonsance imaging (fMRI) data between 50 Seabees with Haley's syndromes and 14 age-, sex-, education-matched controls.

In a series of studies conducted in 2008–2009, Tillman and colleagues attempted to differentiate responses to stimuli in veterans who met the criteria for Haley's three Gulf War illness syndromes. In the first study, Tillman et al. (2010) compared 25 Gulf War veterans from Haley's original cohort of Seabees who reported major cognitive complaints (i.e., the veterans met the criteria for Gulf War illness syndromes 1 or 2) with 23 age- and education-matched Gulf War veterans who were not ill or who reported predominantly peripheral pain symptoms. Event-related potentials as measured by electroencephalographic (EEG) activity were collected while

the veterans performed a go/no go task that required semantic decisions and inhibitory processing (responding to drawing stimuli).

In a further study of event-related potentials for hyperarousal, six veterans who met Haley's criteria for Gulf War illness syndrome 1, eight veterans who had syndrome 2, six veterans who had syndrome 3, and eight control veterans who did not have Gulf War illness performed an auditory three-condition oddball task with gunshot and lion roar sounds as the distractor stimuli (Tillman et al. 2012). Hyperarousal was evaluated with a subset of questions from the Mississippi Scale for Combat-Related PTSD and was measured by means of EEG activity; only 4 of the 20 veterans with Gulf War illness and none of the controls had been diagnosed previously with PTSD. Differences in hyperarousal responses were associated with the Gulf War illness syndromes. In the third study, Tillman and colleagues (2013) had 22 veterans with Gulf War illness (seven with syndrome 1, nine with syndrome 2, and six with syndrome 3) and eight controls perform a visual three-condition oddball task where images authenticated to be associated with the Gulf War were the distractor stimuli. Again, hyperarousal was determined by event-related potentials based on EEG activity. The Volume 10 committee notes that all three studies may have been performed on the same individuals—although there is no explanation as to why the number of veterans in each syndrome category varied—but it is difficult to determine this from the methods described in each paper.

Further testing of this group of veterans with Gulf War illness (11 with syndrome 1, 16 with syndrome 2, and 12 with syndrome 3) and 14 controls used a quantitative sensory testing fMRI protocol to evaluate brain activation in response to innocuous and noxious heat stimuli (Gopinath et al., 2012). Subjects were tested both in the scanner and outside the scanner. Differences in response were seen among the four groups.

U.S. Military Health Survey

A new sample of veterans was selected to further investigate the case definition of the Gulf War illness syndromes identified by Haley and colleagues on the basis of the earlier Seabee studies. While this is a different cohort of veterans, it is discussed here because it includes Haley's original group of Seabees and has been specifically evaluated for the validation of Haley's case definition of Gulf War illness and any associated factors. Because results of this survey were not published until 2011, Volumes 4 and 8 did not report on this cohort of veterans or any derivative studies of them.

Reference Study

To validate the Gulf War illness syndromes posed by Haley et al. (1997b, 2001), Iannacchione et al. (2011) conducted the U.S. Military Health Survey, a study of a population-based sample of more than 8,000 Gulf War deployed and nondeployed (but fit for deployment) service members. The random sample of 14,817 veterans was selected on the basis of 229 sampling strata of demographic and military characteristics. All members of the original Seabee battalion and parents of children with Goldenhar syndrome (a craniofacial abnormality) were included in the sample. The survey, conducted in 2007–2009 by mailed questionnaire and telephone interview, contained questions about symptoms used to develop the syndromes derived by Haley et al. (1997b) and symptoms used for other case definitions—such as that of the CDC—and similar conditions, for example, CFS and fibromyalgia. The telephone interview was completed by 8,020 veterans, a response rate of 60.1%.

The authors did not replicate the exploratory factor analysis conducted by Haley and colleagues to develop their case definitions of Gulf War illness. Rather, the factor weights from

the original Haley et al., study were used to create factor scales and to determine which syndrome fit each person in the study, as was done in both earlier studies of the factor case definition (Haley et al., 1997b, 2001). Results showed similar goodness-of-fit statistics for all three studies. Some 14% of the deployed and 4% of the nondeployed fit any of the six syndromes that make up the factor case definition.

Derivative Studies

Haley and Tuite (2013) explored the association between Gulf War illness (as defined by Haley and also by the CDC) in association with indicators of exposure to chemical warfare agents. Indicators of exposure included self-reports of hearing chemical warfare detection alarms while deployed and modeled exposure to fallout from Khamisiyah based on unit location. This analysis included all 8,020 survey respondents. Results were weighted and reported as a reflection of the entire Gulf War veteran population.

Haley et al. (2013) performed a nested case-control study of 66 veterans who had Gulf War illness syndromes 1, 2, or 3 and 31 control veterans randomly selected from the Military Health Study. Controls were deployed to the Kuwaiti theater of operations but did not meet criteria for Gulf War illness. Participants were admitted to the University of Texas Southwestern Medical Center's Clinical and Translational Research Center where they completed questionnaires and underwent psychologic evaluation, self-reported autonomic symptoms, and completed the following autonomic tests: pupilometry, lacrimation, quantitative sudomotor axon reflexes, heart rate response to deep breathing and the Valsalva maneuver, sensory testing to heat and pain, and blood pressure and heart rate response to head-up tilt. The 24-hour Holter electrocardiography was completed at home.

Hubbard et al. (2014) sought to investigate whether the cholinergic system is impaired in veterans with Gulf War illness by assessing working memory. The investigators combined event-related fMRI results from participants of two studies: 61 veterans with Gulf War illness and 28 matched controls from the sample described by Iannacchione et al. (2011) and 35 veterans with Gulf War illness and 16 matched controls from the sample described by Haley et al. (1997b). Gulf War illness was defined by Haley's syndromes 1, 2, and 3. Controls were matched on age, sex, education, handedness, and rank. Functional MRI was used to examine task-related blood oxygen-level-dependent activity in the dorsolateral and ventrolateral prefrontal cortexes during delayed-response task performance.

Gray et al. Studies

Reference Study

The first in a series of studies by Gray and colleagues (1999a) surveyed Seabees who remained on active duty for at least 3 years after the Gulf War. The Seabees were from 14 commands at two locations (Port Hueneme, California, and Gulfport, Mississippi). Those who were deployed to the Gulf War were in mobile construction battalions performing the same tasks and at the same sites as the reserve Seabee battalion studied by Haley et al. (1997b); however, Gray et al. excluded Gulf War veterans who were no longer on active duty at the time of study.

In 1994, 1,497 study subjects were enrolled: 527 Gulf War veterans and 970 nondeployed veterans. The participation rate of eligible Seabees was 53%. The following were administered to the study participants: an eight-page questionnaire regarding medical history, Gulf War exposures, postwar symptoms, hospitalization, and pregnancy outcomes; questions regarding the

presence of CFS and PTSD; laboratory tests on sera, blood, urine; and pulmonary function and handgrip strength tests.

Derivative Studies

Beginning in May 1997, Gray et al. (2002) distributed a mailed questionnaire to all regular and reserve Navy personnel (n = 18,945) who served on active-duty Seabee command during the Gulf War period. The questionnaire collected information regarding medical history, current health status, symptoms, and environmental exposures such as PB. Of the 17,559 participants who were located, 11,868 completed and returned the survey: 3,831 Gulf War deployed, 4,933 deployed elsewhere, and 4,933 nondeployed.

Knoke et al. (2000) used the same Seabee cohort to conduct a factor analysis of the symptoms reported by the veterans on the Hopkins Symptom Checklist to determine whether there was a unique Gulf War syndrome.

Pennsylvania Air National Guard Study

The Volume 4 committee described an investigation of symptom reporting among members of the Air National Guard in Pennsylvania and two derivative studies. However, no additional derivative studies were identified by the Volume 8 or Volume 10 committees.

Reference Study

In response to requests from DoD, VA, and the Commonwealth of Pennsylvania, in 1995, Fukuda and colleagues (1998) conducted a factor analysis study to assess health status and prevalence and causes of an unexplained illness in Gulf War deployed and nondeployed members of a currently active Pennsylvania Air National Guard unit (n = 667). Three demographically similar Air Force units were used as comparison groups (n = 538, 838, and 1,680). Questionnaires regarding military characteristics, demographics, health status, and 35 specific symptoms previously identified to be of concern were distributed and completed by 3,723 participants (1,163 Gulf War deployed, 2,560 nondeployed). Participation rates were as follows: 62% index unit; 35% unit A; 73% unit B; and 70% unit C. To assess symptom prevalence, investigators combined the four units and compared questionnaire responses of deployed and nondeployed. The authors further studied health outcomes in a subset of participants from the index unit. Of the 490 (45%) deployed members of this unit, 173 (35%) volunteered to participate in the clinical evaluation and completed a mailed clinical questionnaire and the SF-36.

Derivative Studies

A nested case-control study of the same cohort (n = 1,002) sought to identify self-reported exposures associated with cases of CMI (Nisenbaum et al., 2000). Results indicate that meeting the case definition of severe and mild to moderate illness was associated with use of PB, use of insect repellent, and belief in a threat from biologic or chemical weapons. Having an injury requiring medical attention was also associated with having a severe case of CMI. Nisenbaum et al. (2004) conducted a factor analysis of the symptoms reported by the UK Gulf War veterans combined with those reported by the Pennsylvania veterans.

Hawaii and Pennsylvania Active Duty and Reserve Study

The Volume 4 committee described an early study of active duty and reserve personnel stationed in Hawaii and Pennsylvania who had served in the Gulf War, and two derivative studies. However, no additional derivative studies were identified by the Volume 8 or Volume 10 committees.

Reference Study

One of the first epidemiologic studies of U.S. Gulf War veterans was a congressionally mandated study evaluating the psychologic and physical health of active-duty and reserve Army, Navy, Air Force, and Marine Corps personnel from bases in Pennsylvania and Hawaii (Stretch et al., 1995). Questionnaires were mailed to 16,167 potential study participants and inquired about the following: demographics; physical, psychological, and psychosocial symptoms; deployment type; and perceived sources of stress prior to, during, and after combat or deployment. A total of 4,334 veterans returned the questionnaires for a response rate of 31%. Of those, 715 active duty and 766 reserves were deployed to the Gulf War; 1,576 active duty and 948 reserves were not deployed.

Derivative Studies

Two derivative studies of Stretch et al. (1995) were identified. In response to the questionnaire, deployed veterans commonly reported significant levels of stress during deployment, including operating in desert climates, long duty days, extended periods in chemical-protective clothing, lack of sleep, crowding, lack of private time, physical workload, and boredom. Significant levels of stress continued postdeployment (Stretch et al., 1996a). Another publication examined PTSD in this cohort (Stretch et al., 1996b). The prevalence of PTSD symptoms was measured by the Impact of Event Scale and the Brief Symptom Inventory.

New Orleans Reservist Studies

The Volume 4 committee described an investigation of symptom reporting among reservists stationed in New Orleans, and two derivative studies. However, no additional derivative studies were identified by the Volume 8 or Volume 10 committees.

Reference Study

A study by Sutker et al. (1995) and colleagues analyzed psychologic outcomes in a cohort of New Orleans reservists (n = 1,520). The cohort consisted of Louisiana National Guard and reservists from the Army, Air Force, and Navy who had been deployed to combat. Of the 1,272 who responded (overall response rate of 83.7%), 876 had been deployed and 396 had not been deployed. A discriminant function model was used to assess the relationship between personal and environmental resources and psychological outcomes.

Derivative Studies

One derivative study of Sutker et al. (1995) was identified. Assessed by survey at an average of 9 months after the war, veterans completed the Beck Depression Inventory, the Brief Symptom Inventory for Anxiety and Depression, the PTSD checklist, and the Mississippi Scale for PTSD (Brailey et al., 1998).

Multiple Sclerosis Cohort

The Volume 10 committee identified a new cohort of veterans diagnosed with multiple sclerosis (MS), and one derivative study, both published since 2009.

Reference Study

Wallin et al. (2012) identified veterans with MS though VA and DoD disability claims databases. Veterans must have served on active duty between 1990 and 2007. Demographic and medical data were reviewed, and diagnoses were confirmed by study neurologists using standardized criteria. To calculate incidence, the investigators collected annual data on the entire active-duty population between 1990 and 2010 from the Armed Forces Health Surveillance Center. Estimates were stratified by sex, race, and branch of service. The resulting cohort included 2,691 Gulf War era veterans with MS or other clinically isolated syndromes. This cohort is not limited to veterans from the 1990–1991 Gulf War era, and results specific to each era of conflict are not presented. The main limitation of this study may be potential under-ascertainment of cases because any veterans who did not apply for service-connected disability would be missed. Furthermore, because service-connected disability is limited to cases presenting within 7 years of military service, veterans who have MS diagnosed more than 7 years after service may not have applied for service connection. Lastly, this investigation did not consider deployment data, and therefore did not compare MS in deployed versus nondeployed groups.

Derivative Study

A second publication from the same authors (Wallin et al., 2014) looked at the incidence of MS and other demyelinating diseases in Gulf War veterans only and investigated disease risk based on self-reported exposures. This study examined 1,841 MS cases (387 deployed; 1,454 nondeployed) who served in 1990–1991. Deployment characteristics were collected from the DMDC, and exposure to sarin and cyclosarin at Khamisiyah were provided by DoD plume modeling. As with the reference study, these results may be affected by incomplete case ascertainment.

Amyotrophic Lateral Sclerosis Cohort

The Volume 10 committee identified a new cohort of veterans diagnosed with amyotrophic lateral sclerosis (ALS), and one derivative study, both published since 2009.

Reference Study

Horner and colleagues (2003) conducted a nationwide, epidemiologic case-ascertainment study in 1990–1999 to determine if Gulf War veterans have elevated rates of ALS. They used active and passive methods of case ascertainment: active methods included screening of inpatient, outpatient, and pharmacy medical databases from VA and DoD; passive methods included establishment of a toll-free telephone number, solicitations through relevant Internet sites, and mass mailings of study brochures to practicing neurologists in VA and to members of the American Academy of Neurology. ALS diagnosis was verified by a review of medical records.

Of the 2.5 million eligible military personnel, nearly 700,000 had been deployed to the Gulf War. Most of the cases were found with active ascertainment methods. The major study

limitation was potential under-ascertainment of cases, particularly among nondeployed veterans because nondeployed veterans had less incentive to participate. Because of the rarity of ALS, under-ascertainment of a few cases, particularly if the under-ascertainment is greater among the nondeployed, can substantially exaggerate results.

Derivative Studies

Volume 4 noted one study published using the same groups of veterans. The same authors undertook a secondary analysis to address concerns about differential case ascertainment among deployed versus nondeployed veterans. In this secondary analysis, Coffman et al. (2005) assessed case ascertainment bias by estimating the occurrence of ALS employing three capture–recapture analysis methods: log-linear models, sample coverage, and ecologic models. The investigators concluded that there might have been some modest under-ascertainment of cases in nondeployed military personnel but little under-ascertainment in the deployed. Results were corrected for case under-ascertainment.

Volume 8 included a study that extended follow-up for 1 year to December 2001 and investigated temporal patterns of ALS occurrence (Horner et al., 2008). A total of 124 ALS cases were confirmed: 48 among deployed and 76 among nondeployed. The authors emphasized that the follow-up period was still too short to draw any conclusions about ALS in nondeployed military personnel when compared to the general population.

The Volume 10 committee identified one derivative study of these ALS cases. Kasarkis et al. (2009) examined the medical records of 135 cases of ALS diagnosed in deployed and era Gulf War veterans between 1990 and 2002, an additional year of follow-up (28 more cases) beyond that studied by Horner et al. (2008). Details pertaining to diagnoses, age of onset, family history, atypical clinical features, and date of initial ventilation were evaluated by neurologists for 109 veterans for whom medical records were available.

UNITED KINGDOM VETERAN STUDIES

After the United States, the UK provided the most troops for the coalition forces during the Gulf War. The UK veterans have been followed by several research teams. Three reference studies of UK Gulf War veterans were identified in Volume 4. Two teams of researchers in the UK studied separate, nonoverlapping, stratified random samples of the over 53,000 military personnel sent to the Gulf War. The first team was from the University of London (Guy's, King's, and St. Thomas Medical Schools) (Unwin et al. 1999); the second team was from the University of Manchester (Cherry et al., 2001a,b). In addition, a third team of researchers from the London School of Hygiene and Tropical Medicine surveyed the entire cohort of 53,000 veterans examining birth defects and other reproductive outcomes (Maconochie et al., 2003). The Volume 8 committee identified only one new derivative study that was based on the University of London cohort study. No new studies pertaining to the UK veterans were identified by the Volume 10 committee.

Although not traditional cohort studies per se, UK Defence Analytical Services Agency has periodically assessed the rates and causes of mortality for the entire population of UK Gulf War veterans. The Statistical Notices provide summary statistics on the causes of deaths that have occurred since April 1, 1991. The mortality rates of 53,409 UK Gulf veterans are compared with an era cohort of 53,143 UK Armed Forces personnel of similar age, gender, service, rank, and regular/reservist status who were in service on January 1, 1991 but who did not deploy to the

gulf. The statistics include those who died while in service and those who died after they had left the services and are based on deaths reported to the Ministry of Defence. These notices are cited in Chapter 4 in the section on mortality (DASA, 2005, 2009, 2015).

University of London Veteran Studies

Reference Study

At the University of London, Unwin and colleagues (1999) studied the health effects of deployment by randomly sampling the entire UK contingent deployed to the Gulf War (n = 53,462)[6]; the control groups consisted of those deployed to the conflict in Bosnia (n = 39,217) and service members who were deployed in the same period to noncombat locations outside the UK (n = 250,000). The era control group was recruited from a subset of nondeployed service members who were fit for combat duty, thus avoiding selection bias related to the healthy warrior effect. Investigators distributed a mailed questionnaire that asked about symptoms (50 items), medical disorders (39 items), exposure history (29 items), functional capacity, and other topics. Potential confounding factors (including sociodemographic and lifestyle factors) were controlled for in multiple logistic regression analysis. Response rates were as follows: 70.4% Gulf War deployed, 61.9% Bosnia cohort, and 62.9% era cohort. The Gulf War deployed veterans reported a higher prevalence of symptoms and diminished functioning than did either comparison group.

The UK Gulf War cohorts completed a second questionnaire with details of the dates they were deployed to each location and the exposures they had experienced. The questionnaire listed 14 exposures, such as combat exposure, number of inoculations, number of days handling pesticides, days exposed to smoke from oil-well fires, and duration of stay in the gulf region. The main analysis involved a multiple regression of each of the seven factors identified through factor analysis on all exposures and other potential confounders. Many of the reported exposures correlated with one another.

Derivative Studies

Nine derivative studies of this cohort were described in Volume 4 (Hotopf et al., 2003a,b; Macfarlane et al., 2000, 2003, 2005; Reid et al., 2001; Rose et al., 2004; Sharief et al., 2002; Nisenbaum et al., 2004). The Volume 8 committee identified two new studies of this cohort (Stimpson et al., 2006; Ismail et al., 2008).

A follow-up study using a mailed survey was sent 11 years after the war to a stratified random sample of 3,305 participants (1,472 Gulf War deployed, 909 Bosnian deployed, 924 era veterans) from the total who completed the first study. The response rates were as follows: 74.0% Gulf War deployed, 70.2% Bosnia deployed, and 69.7% era veterans. To assess physical symptoms, respondents completed the SF-36. Receiving multiple vaccinations during deployment was weakly associated with five of the six health outcomes, including CMI (as defined by CDC) (Hotopf et al., 2003a). Hotopf et al. (2003b) studied a subset of these veterans to assess paraoxonase-1 activity and genotype for paraoxonase-1–55 and paraoxonase-1–192. Four groups were selected: deployed veterans who reported physical symptoms after the war (n =

[6] UK military personnel in the Gulf War were somewhat different from U.S. personnel in demographics, combat experience, and exposures to particular agents (United Kingdom Ministry of Defence, 2000).

115); healthy deployed veterans (n = 95); symptomatic Bosnia peacekeeping veterans (n = 52); and symptomatic nondeployed military controls (n = 85).

Macfarlane and colleagues (2000) assessed mortality of the entire UK cohort of deployed veterans (n = 53,462) compared with frequency matched controls; the follow-up period was from the end of the Gulf War (April 1, 1991) to March 31, 1999. Results from a further 13-year follow-up (ending June 30, 2004) of the same cohort remained consistent (Macfarlane et al., 2005). The later study examined self-reported exposures (taken from the earlier morbidity studies in 1997–2001) and mortality in the population of UK Gulf War deployed veterans.

Incidence of cancer, as identified by the National Health Service register, was determined based on follow-up from the end of the Gulf War until July 31, 2002, for all deployed UK service members compared with nondeployed matched controls (era veterans). Of the 51,721 Gulf War veterans included in this analysis, 270 were diagnosed with cancer; of the 50,755 era veterans included in this analysis, 269 were diagnosed (Macfarlane et al., 2003).

Another separate analysis of a subgroup of veterans meeting case criteria for MCS symptoms assed whether they were more likely to report several types of pesticide exposures (Reid et al., 2001).

Rose et al. (2004) and Sharief et al. (2002) conducted a case-control study examining neuromuscular symptoms in 49 Gulf War veterans with more than four neuromuscular symptoms and lower functioning according to the SF-36 compared with 26 healthy Gulf War deployed veterans, 13 symptomatic Bosnia deployed veterans, and 22 symptomatic nondeployed controls. They tested peripheral nerves, skeletal muscles, or neuromuscular junctions.

Nisenbaum et al. (2004) used factor analysis on symptom data from both the UK reference study and the Pennsylvania Air Force unit study (Fukuda et al., 1998; discussed later in this chapter) to look at the interrelationships between symptoms. Each sample was split in half to provide an exploratory and a confirmatory sample. Four correlated factors were identified in each of the samples: respiratory, mood-cognition, gastrointestinal/urogenital, and peripheral nervous.

The Volume 8 committee identified two new studies based on the University of London study. Stimpson and colleagues (2006) used the same population and methods described in Unwin et al. (1999) to specifically examine the prevalence of reported pain and its association with deployment status. Ismail and colleagues (2008) assessed the prevalence of CFS by implementing a two-phase study approach that was a continuum of the Unwin et al. (1999) (phase I) cohort above. Phase II consisted of a random sampling of the 244 veterans (Gulf War and Bosnia deployed, and era veterans) who screened positive for a physical disability (score less than or equal to 72.2 on the SF-36) in the Unwin study; 111 (45.5%) were Gulf War deployed and 133 (54.5%) were nondeployed veterans (Bosnia: n = 54, era: n = 79).

University of Manchester Veteran Study

Seven years after the Gulf War, the University of Manchester study surveyed a random sample of all UK veterans, distinct from that of Unwin et al. (1999), who deployed between September 1990 and June 1991, as identified by the Ministry of Defense (Cherry et al., 2001a,b). Eligible deployed veterans (n = 9,505) were divided into two groups—main cohort (n = 4,755) and validation cohort (n = 4,750) to permit replication of analysis and to assess consistency. The control population (n = 4,749) was nondeployed veterans in good general health. Veterans were sent a questionnaire about the extent to which they were burdened, within the last month, by any

of 95 symptoms. By asking them to mark their answers on a visual analogue scale, investigators sought to determine the degree of symptom severity. Investigators also sought to determine areas of peripheral neuropathy by asking veterans to shade body areas on two mannequins in which they were experiencing pain or numbness and tingling

No derivative studies were identified for this UK cohort.

London School of Hygiene and Tropical Medicine Veteran Study

Reference Study

The third UK study was a very large mail survey that began in August 1998 (with reminders until 2001) (Maconochie et al., 2003). The study was designed to assess reproductive outcomes among Gulf War veterans and also contained open-ended questions regarding general health. The exposed cohort consisted of all UK Gulf War veterans, and the unexposed cohort consisted of a random sample of nondeployed UK military personnel from the same period. Although the participation rates were low (47.3% and 37.5% of male and female Gulf War veterans, respectively, and 57.3% and 45.6% of male and female nondeployed veterans), 25,084 Gulf War veterans and 19,003 nondeployed veterans returned survey responses. The survey included items on reproductive and child health, exposure history, current health, and health of sexual partners; it was supplemented by examination of medical records for pregnancies, live births, and outcomes. Male participants (n = 42,818) reported 27,929 pregnancies in their partners, and female participants (n = 1,269) reported 861 pregnancies. Reports of miscarriages and congenital malformation were clinically validated.

Derivative Studies

Three derivative studies were described in Volume 4; no new derivative studies were identified by the Volume 8 committee.

Based on results of Maconochie et al. (2003), Doyle et al. (2004) examined the associations between risk of miscarriage, stillbirth, or congenital malformations for deployed and nondeployed women. Maconochie et al. (2004) assessed the risk of infertility in male Gulf War veterans (females were not included in study); self-reports were validated with clinical diagnosis.

In a subanalysis of the population defined by Maconochie et al. (2004), Simmons et al. (2004) described new symptoms and medical conditions reported by deployed and nondeployed veterans.

No additional derivative studies were identified by the Volume 10 committee.

AUSTRALIAN VETERAN STUDIES

A national study of all Australian Gulf War veterans conducted in 2000–2002 (Sim et al., 2003) has been extensively assessed and the cohort followed since the initial study. Six derivative studies were described in Volume 4 (Kelsall et al., 2004a,b, 2005; Ikin et al., 2004; McKenzie et al., 2004; Forbes et al., 2004), and the Volume 8 committee identified two new derivative studies (Kelsall et al., 2006, 2007). The Volume 10 committee identified two derivative studies based on the original investigation (Kelsall et al., 2009, 2014), a report detailing the results of a recent follow-up assessment conducted in 2011–2012 (Sim et al., 2015),

and two publications analyzing data from that follow-up assessment (Ikin et al., 2015; Gwini et al., 2015).

Reference Study

Investigators from Monash University in Australia conducted the Australian Gulf War Veterans' Health Study by examining all 1,871 Australian veterans deployed to the Gulf War region from August 2, 1990, to September 4, 1991; naval personnel made up 86.5% of this cohort (Sim et al., 2003). The control group consisted of 2,924 nondeployed Australian Defence Force personnel matched by service type, sex, age, and military status. Participation rates were 81% (n = 1456) for the deployed and 57% (n = 1588) for the control group.

A mailed questionnaire was distributed in 2000–2002, which included the SF-12, General Health Questionnaire (GHQ)-12, and questions regarding physical and psychological health, military service history, and exposures during deployment. In addition, participants were asked to attend one of 10 Health Services Australia medical clinics to undergo a comprehensive health assessment, a full physical examination, blood work, and fitness tests. Interview-administered questionnaires such as the Composite International Diagnostic Interview (CIDI) were given to all participants to assess mental health (Sim et al., 2003). Gulf War veterans reported more general health symptoms and more severe symptoms than the nondeployed controls.

Derivative Studies

Kelsall et al. (2004a) reported the prevalence and severity of symptoms experienced by veterans assessed by Sim et al. (2003). Ikin et al. (2004) used responses to the CIDI and a service experience questionnaire to assess the relationship between the presence of a psychiatric disorder and the veterans' perceptions of stressors during deployment. Very few personnel experienced direct combat; however, despite their lack of combat exposure, deployment was a stressful event with veterans experiencing higher rates of fear and threat of entrapment, attack (including nerve agent warfare), and death or injury. In a follow-up study, Ikin et al. (2005) reported associations between stressful experiences and demographic and deployment characteristics.

McKenzie et al. (2004) reported on the psychological health and stressful experiences of Australian Gulf War veterans using three standard instruments to measure functioning and psychological health. Symptom severity associated with Gulf War exposures (vaccinations, PB, pesticides and insect repellants, chemical weapons, and stressful situations) was assessed by Kelsall and colleagues (2004a). Kelsall et al. (2004b) also assessed the respiratory health status of a random sample of the veterans using a questionnaire, spirometric testing, and a physical examination. Health status was assessed in relation to reported exposure to smoke from the Kuwaiti oil-well fires and dust storms.

In 2005, Kelsall et al. studied the neurological status of the Australian cohort. Of the 1,424 deployed veterans who completed the mailed questionnaire, 1,382 undertook the neurological examination; 1,376 of the 1,548 controls completed both the questionnaire and neurological examination (described in Sim et al., 2003 above).

Forbes et al. (2004) used factor analysis to attempt to group symptom complexes for this cohort. This study confirms the greater extent and severity of symptoms in Gulf War veterans, even in a predominantly naval population with few direct military attacks, no deaths, and few casualties.

The Volume 8 committee identified two additional derivative studies of the Australian Gulf War veterans. Kelsall et al. (2006) conducted a study on the prevalence of CFS from August 2000 to April 2002. The participation rates were as follows: 80.5% (1,456) of the 1,808 eligible veterans and 56.8% (1,588) of 2,796 controls. Of those, 1,384 deployed veterans and 1,379 controls completed both the mailed questionnaire and medical assessment. In addition to questions on general health, fitness tests, laboratory work, and pulmonary function, clinical examiners specifically inquired about any tiredness or fatigue following normal activities and its duration within the last 12 months.

Male reproductive health was assessed for the 1,424 deployed and 1,548 nondeployed veterans who completed the mailed questionnaire; response rates were as noted in Kelsall et al. (2006). Questions of interest included those related to pregnancy outcomes (live birth, miscarriage, stillbirth), and for live births, participants were asked about date, weight, gestation, and birth defects (Kelsall et al., 2007).

Five new studies based on the Australian Gulf War Veterans' Health Study cohort were identified by the Volume 10 committee.

Kelsall et al. (2009) assessed comorbidities associated with Gulf War illness among 1,381 eligible Australian male veterans who had deployed to the Gulf War, a comparison group of 1,085 veterans who had been on active service during the war but had not deployed, and 292 veterans who had deployed elsewhere during the war. All the veterans completed a 63-item symptom questionnaire, as well as the GHQ-12, the SF-12, and the Alcohol Use Disorders Identification Test. Veterans also received an in-person health assessment that included a full physical examination, with lung function and fitness tests, and a mental health assessment using the psychologist-administered, computer-assisted CIDI. Multisymptom illness was defined using a modification of the CDC definition.

In another study, Kelsall et al. (2014) compared the 1,381 Australian veterans with 1,377 veterans who were serving in the military at the time or had previously deployed. The assessment queried veterans about doctor-diagnosed arthritis or rheumatism, back or neck problems, joint problems, and soft tissue disorders. Medical practitioners then rated the self-reported diagnoses as nonmedical, unlikely, possible, or probable; only probable diagnoses were analyzed. This approach added a level of medical judgment to the self-reports but did not verify the self-reported diagnoses with a clinical evaluation.

Sim et al. (2015) reported the results of the Australian Gulf War Veterans' Follow-Up Health Study. This assessment was conducted in 2011–2013, and all participants of the original 2003 study were eligible to participate; 715 Gulf War veterans and 675 comparison group veterans participated in the follow-up study (50% participation rate). The follow-up study collected much of the same information as the original study, but it also inquired about additional outcomes including pain, sleep disturbance, injury, musculoskeletal disorders, demoralization, and measures of well-being (quality of life, life satisfaction, life events, financial distress, suicidal ideation, and community participation). The follow-up also extended exposure assessment efforts from those used in the baseline study. Data were collected by mailed questionnaire, telephone interview, collection of Department of Veterans Affairs' health data, and claims history from Medicare, Pharmaceutical Benefits Scheme, and Repatriation Pharmaceutical Benefits Scheme. Other databases included national mortality and cancer registries and information from the baseline study.

Ikin et al., (2015) reported additional results of the Australian follow-up study compared to the results of the previous survey. Depression and depression symptoms were measured by the

CIDI and other heath questions included in the survey. The authors compared depression measured in the baseline survey (Ikin et al., 2004) to responses collected in the latest survey to report patterns of persistence, remittance, and new onset depression. The analyses included 715 Gulf War veterans and 675 nondeployed veterans (about a 50% participation rate).

To assess the persistence of symptoms in Gulf War veterans, Gwini et al. (2015) compared responses to a 63-item symptom checklist in the first survey (Sim et al., 2003) and the second survey (Sim et al., 2015). Fifty-four percent of veterans and 47% of comparison veterans surveyed responded to the second survey. The analysis adjusted for age, rank, and branch of service. The authors made three main comparisons: between groups to show longitudinal change; symptoms reported in the second survey among respondents who reported symptoms in the first survey to show persistence; and new symptoms reported by respondents who did not report symptoms in the first survey to show incidence.

DANISH PEACEKEEPER STUDIES

Danish service members were sent to the Persian Gulf at the end of the Gulf War as peacekeepers (Ishoy et al., 1999b). Volume 4 cited four derivative studies based on the initial cohort. Neither the Volume 8 nor the Volume 10 committees identified any additional derivative studies on Danish Gulf War veterans.

Reference Study

Military personnel from Denmark were involved in peacekeeping or humanitarian missions occurring predominantly after the Gulf War ceasefire, but were located in the same areas as other coalition forces who served in Gulf War combat (Ishoy et al., 1999b). A total of 821 Danes, deployed between August 1990 and December 1997, were eligible for inclusion in this population-based cohort; 686 (83.6%) agreed to participate in the study. The deployed veterans were matched by age, sex, and profession to 400 members of the Danish armed forces who were not deployed to the Gulf War; the participation rate was 57.8% (n = 231). Participants completed a detailed questionnaire that included 22 neuropsychologic symptoms, and then participants received detailed clinical health and laboratory examinations (e.g., height, weight, blood pressure, battery of urinary and blood work, battery of neuropsychologic tests) and physician interviews about their medical history and symptoms. Gulf War participants were also asked about their exposures while in the gulf. The examinations were conducted between 1997 and 1998.

Derivative Studies

Proctor et al. (2003) assessed neuropsychologic symptoms in the Danish Gulf War veterans. Gastrointestinal symptoms and diseases and symptoms related to the skin or allergies were evaluated by Ishoy et al. (1999a) in relation to specific Gulf War exposures. The investigators also examined male participants for sexual dysfunction and reproductive health. Self-reports of sexual problems were validated with medical examinations and laboratory testing, such as reproductive hormone parameters (Ishoy et al., 2001a,b).

One analysis investigated whether 22 neuropsychologic symptoms were associated with 18 self-reported environmental exposures (physical, chemical, biologic exposures and psychological stressors) (Suadicani et al., 1999).[7]

CANADIAN VETERANS STUDY

In Volume 4, the Canadian Gulf War Veterans Study was not included in the presentation of major cohort studies. The Canadian study (Goss Gilroy Inc., 1998) was considered to be a secondary study in Volume 4, and the Volume 8 committee agreed with that classification because the study relied on self-reports gathered through a mailed questionnaire. The Volume 8 committee identified one new study based on the Canadian Gulf War veterans (Statistics Canada, 2005), although it is unclear if the cohort in the new study was the same as that studied by Goss Gilroy. The Volume 10 committee did not find any additional studies of this cohort.

Reference Study

The Canadian Department of National Defence tasked Goss Gilroy (1998) to compare the overall health status and prevalence of symptoms in all Canadian Forces personnel who deployed to the Gulf War conflict with a representative sample of Canadian personnel who served in the military at the same time but who had not been deployed to the Persian Gulf. Military personnel were also compared with the general population as represented by the 1990 Ontario Health Survey. A questionnaire was mailed out to 9,947 participants in 1997 and included information on sociodemographic factors, medical history and current status, and Gulf War deployment and exposure. The response rates were 73% (n = 3,113) for the Gulf War deployed and 60.3% (n = 3,439) for the deployed elsewhere controls. The report described the effects of confounders such as income and rank and presented associations between Gulf War exposures and self-reported adverse health outcomes (Goss Gilroy Inc., 1998).

Derivative Study

A 9-year follow-up study was conducted on mortality and cancer incidence in the cohort of deployed Canadian personnel (n = 5,117) compared to Canadian Forces who were eligible but not deployed to the gulf (n = 6,093). The national mortality database and national cancer registry provided the information necessary for record linkage. There were 42 deaths in the deployed cohort and 54 deaths in the nondeployed (Statistics Canada, 2005).

SUMMARY

As the committee organized the broad body of evidence described above, they made several overarching observations. First, there are numerous studies by various researchers on Gulf War veterans from several countries, but these studies are all limited by a few common factors, such as lack of exposure data or reliance on self-reported outcomes, that can never be overcome. As a result there will continue to be gaps in the epidemiologic literature on these

[7] Exposures did not include pyridostigmine bromide or vaccinations against chemical or biologic warfare agents, because Danish veterans had a peacekeeping role and thus were not at risk for chemical or biologic warfare.

cohorts that may never be resolved. Second, sex-specific and race/ethnicity-specific data are rarely reported. Even though women are oversampled in some studies such as those conducted by the VA (Kang et al., 2000, 2009; Bossarte, 2014; Dursa et al., 2016) they are excluded from analyses in others (for example, studies of the Australian cohort). VA also oversamples other groups such as National Guard and reservists, and results for these groups are occasionally but not always reported separately. Race and ethnicity are usually adjusted for in analyses but are otherwise virtually ignored by the studies discussed in this chapter. Lastly, many derivative studies have moved from characterizing the health of veterans to looking for etiology and biomarkers of certain health conditions (such as use of fMRI in Gulf War illness). Those studies are discussed briefly in Chapter 4 in the section on Gulf War illness.

TABLE 3-1 Reference and Derivative Studies for the Major Gulf War Cohorts

Cohort/Reference Study	Derivatives	Purpose/Outcome
VA National Health Survey of Gulf War Veterans and Their Families, Kang et al., 2000		
Volume 4	Davis et al., 2004	Presence of distal symmetric polyneuropathy
	Eisen et al., 2005	Numerous health outcomes and general health assessment
	Kang et al., 2001	Self-reported birth defects
	Kang et al., 2002	Association of symptom clusters with self-reported exposures
	Kang et al., 2003	Prevalence of PTSD and chronic fatigue syndrome
	Kang et al., 2005	Role of sexual assault and harassment on the risk of PTSD
	Karlinsky et al., 2004	Pulmonary function and self-reported respiratory symptoms
Volume 8	Blanchard et al., 2005	Prevalence of chronic multisymptom illness
	Page et al., 2005a,b	Possible exposure at Khamisiyah and self-reported morbidity
	Toomey et al., 2007	Prevalence of psychiatric disorders, symptom self-report, and quality-of-life status
	Kang et al., 2009	Self-reported general health status
	Toomey et al., 2009	Neuropsychological functioning
New	Wallin et al., 2009	Neuropsychological performance and quality of life
	Coughlin et al., 2011a	Relationship between obesity, PTSD, CFS-like illness, and multisymptom illness
	Coughlin et al., 2011b	Relationship between alcohol use and PTSD, depression, multisymptom illness, and CFS-like illness
	Li et al., 2011a	Prevalence, incidence, and persistence of self-reported health outcomes and health status
	Bossarte, 2014; Dursa et al., 2016	Self-reported health conditions and symptoms
	Li et al., 2014	Autonomic function in veterans with Gulf War illness
Iowa Veterans/Iowa Persian Gulf Study Group, 1997		
Volume 4	Black et al., 1999	Impact of multiple chemical sensitivity on quality of life and utilization of health services
	Black et al., 2000	Risk factors and prevalence of multiple chemical sensitivity
	Doebbling et al., 2000	Factor analysis of self-reported symptoms (definition of Persian Gulf War syndrome)
	Zwerling et al., 2000	Prevalence of self-reported postwar injuries

Cohort/Reference Study	Derivatives	Purpose/Outcome
	Barrett et al., 2002	Association between PTSD and self-reported physical health issues
	Lange et al., 2002	Exposure to Kuwait oil fires and risk of asthma and bronchitis
	Black et al., 2004a	Prevalence of psychiatric disorders
	Black et al., 2004b	Prevalence and risk factors for anxiety disorders
Volume 8	Ang et al., 2006	Identification of predictors of chronic widespread pain
	Black et al., 2006	Prevalence of borderline personality disorder
	Forman-Hoffman et al., 2007	Prevalence of self-reports of symptoms of chronic widespread pain
New	None	
Oregon and Washington Veterans, McCauley et al., 1999a		
Volume 4	Bourdette et al., 2001	Prevalence of unexplained illness
	Spencer et al., 2001	Self-reported exposure and unexplained illness
Volume 8	None	
New	None	
Kansas Veterans Study, Steele et al., 2000		
Volume 4	None	
Volume 8	None	
New	Steele et al., 2012	Wartime exposures related to Gulf War Illness
	Steele et al., 2015	Butyrylcholinesterase genotype and gene-exposure interaction in Gulf War illness
Ft. Devens and New Orleans Cohorts, Proctor et al., 1998		
Volume 4	Proctor et al., 2001a	Assessment of health-related quality of life
	Proctor et al., 2001b	Overlap between symptoms of chronic fatigue and chemical sensitivity, and the case definition for chronic multisymptom illness
	White et al., 2001	Self-reported exposure and neuropsychological functioning
Volume 8	Proctor et al., 2006	Possible exposure at Khamisiyah and neuropsychological functioning

Cohort/Reference Study	Derivatives	Purpose/Outcome
New	None	
Seabees, Haley et al., 1997b		
Volume 4	Haley et al., 1997a; Haley and Kurt, 1997	Self-reported exposure to neurotoxicants and nervous system-based syndromes
	Haley et al., 1999	Genetic susceptibility and risk of neurologic damage
Volume 8	Haley et al., 2000a,b	Basal ganglia injury
	Roland et al., 2000	Vestibular function
	Haley et al., 2004	Autonomic function
	Haley et al., 2009	Regional cerebral blood flow
New	Li et al., 2011b	Hippocampal blood flow assessed by MRI
	Liu et al., 2011	Cerebral blood flow assessed by MRI
	Gopinath et al., 2012	Sensory and pain processing assessed by fMRI
	Odegard et al., 2013	Memory impairment assessed by fMRI
	Tillman et al., 2010, 2012, 2013	Event-related potentials in response to stimuli
	Moffett et al., 2015	Impairments in complex language assessed by fMRI
U.S. Military Health Survey, Iannacchione et al., 2011		
New	Haley et al., 2013	Measures of cholinergic autonomic dysfunction in Gulf War illness
	Haley and Tuite, 2013	Indicators of exposure to chemical warfare and Gulf War illness
	Hubbard et al., 2014	Executive functioning assessed by fMRI
Seabees, Gray et al., 1999a		
Volume 4	Gray et al., 2002	Self-report of symptoms and general health status
	Knoke et al., 2000	Self-report of symptoms
Volume 8	None	
New	None	

Cohort/Reference Study	Derivatives	Purpose/Outcome
Pennsylvania Air National Guard Veterans, Fukuda et al., 1998		
Volume 4	Nisenbaum et al., 2000	Self-reported exposures and chronic multisymptom illness
	Nisenbaum et al., 2004	Factor analysis of self-reported symptoms
Volume 8	None	
New	None	
Hawaii and Pennsylvania Active-Duty and Reserve, Stretch et al., 1995		
Volume 4	Stretch et al., 1996a	Prevalence of psychiatric disorders
	Stretch et al., 1996b	Prevalence of PTSD
Volume 8	None	
New	None	
New Orleans Reservists, Sutker et al., 1995		
Volume 4	Sutker et al., 1995	Prevalence of psychologic disorders
	Brailey et al., 1998	Prevalence of psychiatric disorders
Volume 8	None	
New	None	
Multiple Sclerosis Cohort, Wallin et al., 2012		
New	Wallin et al., 2014	Risk of multiple sclerosis
Amyotrophic Lateral Sclerosis Cohort, Horner et al., 2003		
Volume 4	Coffman et al., 2005	Risk of ALS
Volume 8	Horner et al., 2008	Risk of ALS
New	Kasarkis et al., 2009	Clinical features of ALS

Cohort/Reference Study	Derivatives	Purpose/Outcome
UK Veterans: University of London, Unwin et al., 1999		
Volume 4	Macfarlane et al., 2000	Self-reported exposure and mortality
	Reid et al., 2001	Self-reported exposure and multiple chemical sensitivity and chronic fatigue syndrome
	Sharif et al., 2002	Neuromuscular symptoms evaluated through objective tests
	Hotopf et al., 2003a,b	Neurologic assessments
	Macfarlane et al., 2003	Incidence of cancer
	Nisenbaum et al., 2004	Factor analysis of self-reported symptoms
	Rose et al., 2004	Neuromuscular symptoms evaluated through objective tests
	Macfarlane et al., 2005	Self-reported exposure and mortality
Volume 8	Stimpson et al., 2006	Self-report of chronic widespread pain
	Ismail et al., 2008	Prevalence of chronic fatigue and related disorders through assessment
New	None	
UK Veterans: University of Manchester, Cherry et al., 2001a,b		
Volume 4	None	
Volume 8	None	
New	None	
UK Veterans: London School of Hygiene and Tropical Medicine, Maconochie et al., 2003		
Volume 4	Doyle et al., 2004	Prevalence of miscarriage, stillbirth, and congenital malformations
	Maconochie et al., 2004	Self-report of fertility problems
	Simmons et al., 2004	Self-report of medical symptoms or disease
Volume 8	None	
New	None	

Cohort/Reference Study	Derivatives	Purpose/Outcome
Australian Veterans, Sim et al., 2003		
Volume 4	Forbes et al., 2004	Factor analysis of self-reported symptoms
	Ikin et al., 2004	Prevalence of psychiatric disorders
	Kelsall et al., 2004a	Association between self-reported exposures with numerous symptoms and medical conditions
	Kelsall et al., 2004b	Self-reported exposure and respiratory health status
	Mckenzie et al., 2004	Psychological health and functioning
	Kelsall et al., 2005	Self-report of exposures and neurological symptoms
Volume 8	Kelsall et al., 2006	Self-reported exposure and prevalence of chronic fatigue syndrome
	Kelsall et al., 2007	Self-reported birth defects and other pregnancy outcomes
New	Kelsall et al., 2009	Comorbidities of multisymptom illness
	Kelsall et al., 2014	Psychological comorbidities of musculoskeletal disorders
	Gwini et al., 2015	Prevalence, persistence, and incidence of symptoms
	Sim et al., 2015	Australian Gulf War Veterans' Follow-Up Health Study—all health outcomes
Danish Peacekeepers, Ishoy et al., 1999b		
Volume 4	Ishoy et al., 1999a	Prevalence of gastrointestinal symptoms and diseases, skin disease, and respiratory symptoms and function
	Ishoy et al., 2001a,b	Self-report of sexual dysfunction and birth defects
	Proctor et al., 2003	Prevalence of neuropsychiatric symptoms and neurobehavioral performance
Volume 8	None	
New	None	
Canadian Veterans, Goss Gilroy Inc., 1998		
Volume 4	None	
Volume 8	Statistics Canada, 2005	Mortality rate and cancer incidence
New	None	

4

EVALUATION OF HEALTH CONDITIONS

Veterans who were deployed to the Persian Gulf region in 1990–1991 have consistently reported having poorer health and quality of life than veterans who served in the military during the war but were not deployed or were deployed elsewhere. This increase in adverse health effects has been seen not only in U.S. veterans, but also in veterans of the coalition forces, including the UK, Australia, Canada, and Denmark. As noted in Chapter 1, these service members were exposed to a multitude of chemicals, vaccinations, and adverse environmental conditions that individually or in concert may be harmful to a few or many service members.

In this chapter, each health condition section starts with an overview of the condition, then a brief summary of the Volumes 4 and 8 findings and conclusions, followed by a review of the new literature where available, and then a summary of the Volume 10 committee's findings and conclusions. Each section ends with a summary table of the primary studies from Volumes 4 and 8 as well as any new primary studies cited in this volume. All health conditions addressed in Volume 8 are covered here; if new literature was not identified, this is indicated. In the last section of this chapter, the committee describes the only veteran studies that had objective exposure measures, that is, to depleted uranium (DU); no summary table is included for these primary studies, although they are described in the text.

Some health conditions discussed individually in Volume 8 were combined in this volume. The section on women's health from Volume 8 is not mirrored in this volume; if information specific to women's health conditions was identified it was included in the relevant health condition section. Fibromyalgia, chronic widespread pain, chronic fatigue syndrome (CFS), and conditions of the musculoskeletal system are all now discussed in the section on pain-related conditions. Although, the health conditions generally are presented in the same order as Volume 8, the names of some of the sections have been slightly modified and the terminology of the *International Statistical Classification of Diseases and Related Health Problems,* 10th edition, is no longer used. Finally the section on chronic multisymptom illness is now called Gulf War illness in keeping with the suggestion of prior Institute of Medicine (IOM) committees (IOM, 2010, 2014a). All cancers, regardless of the organ system affected, are discussed in the section on cancer rather than in the section on the affected organ system. Similarly, all studies on mortality, whether from external causes or from disease, are now discussed in the section on causes of mortality.

Information on the committee's process and criteria for identifying, reviewing, and categorizing the literature, as well as description of the categories of association the committee used, may be found in Chapter 2. It should be noted that not all studies were classified the same way for each health condition. A study may be classified as a primary study for one health condition because of the method used to obtain the data, but the same study may be classified as

secondary for another health condition if less rigorous methods were used to assess that condition. The committee indicates in each section why a particular study was classified as primary, secondary, or was best described in the subsection "Other Related Studies."

The Volume 10 committee relied on human epidemiologic studies to draw its conclusions about the strength of evidence regarding associations between deployment to the Gulf War and health conditions seen in Gulf War veterans. A major problem with comparing rates of health conditions in deployed cohorts versus nondeployed military cohorts or versus the general public is the so-called "healthy-warrior effect," (see Chapter 2 for a description) which may underestimate effects on veterans. Inasmuch as military personnel must meet physical-health criteria when they enter the military and while they are on active duty, particularly when deployed, the group's health status is usually better than that of their nondeployed counterparts or the general population of the same age and sex.

Further complicating the assessment of Gulf War veterans' health is that in recent years, the diagnostic criteria or definitions for several of the health conditions discussed in this volume have been revised to reflect the evolving understanding of these conditions brought on by scientific and other advances. These types of changes are normal in medical science, and it is likely that the diagnostic criteria for these conditions will further change in the future as knowledge about them grows.

Among those health outcomes with recently changed criteria are mental health disorders, fibromyalgia, chronic fatigue syndrome, and Gulf War illness. Although none of the studies discussed in this report have used the revised diagnostic criteria for mental health disorders, fibromyalgia, and chronic fatigue syndrome, there are research implications as the new criteria are adopted and implemented. As future bodies review and compare studies using the old criteria and new diagnostic criteria, there may be differences in the incidence or prevalence of a condition that may result from the use of the revised criteria. For example, the new diagnostic criteria for autism resulted in a lower prevalence estimate of the condition than the old criteria (Maenner et al., 2014). The revised criteria for these conditions are briefly discussed in the relevant sections below.

GULF WAR ILLNESS

Shortly after Gulf War veterans returned from their deployments to the Persian Gulf region, many of them began complaining of a broad range of symptoms that did not have an obvious, documentable etiology and pathophysiology. This reporting of symptoms was seen not only in U.S. veterans who had been exposed to many chemicals, including possibly nerve agents from the demolition at Khamisiyah, but Gulf War veterans from coalition countries, including the UK, Denmark, Australia, and Canada, also reported an increase in numerous symptoms. Many of the coalition forces were in the Persian Gulf region after Khamisiyah or were otherwise unlikely to have been exposed to nerve agents. Since the mid-1990s, numerous studies have documented that deployment to the Gulf War in 1990–1991 entailed an increased risk of developing a multitude of symptoms that veterans themselves called "Gulf War illness" or "Gulf War syndrome." Although exact numbers are not available, it has been estimated that as many as one-third of the Gulf War deployed veterans may have Gulf War illness (RAC, 2014) and in the recent survey of the National Cohort of Gulf War and Gulf Era Veterans, Dursa et al. (2016) estimated that as of 2013 approximately 44% of deployed veterans reported having chronic

multisymptom illness compared with 20% of the era veterans (weighted estimates). Studies have consistently shown that deployed Gulf War veterans have a higher number and greater severity of symptoms compared with nondeployed and era veterans (IOM, 2010). The cause of and treatment interventions for Gulf War illness have been addressed by several previous IOM committees (IOM, 2000, 2006b, 2010, 2014b), by the Department of Veterans Affairs (VA) Research Advisory Committee on Gulf War Veterans' Illnesses (RAC), and by numerous researchers. Several difficulties persist in studying this illness, including the many different methods used for identifying cases and the variable presentations and complex manifestations. All primary studies of Gulf War illness are summarized in Table 4-1at the end of this section.

Definitions of Gulf War Illness

The proper term to use when describing the complex set of symptoms experienced by Gulf War veterans has been the subject of considerable discussion. This conglomeration of symptom clusters linked to various organ systems has been called chronic multisymptom illness by VA (Kang et al., 2009). However, several alternate definitions and suggestions for classifying these syndromes have been proposed, including those of the Centers for Disease Control and Prevention (CDC) (Fukuda et al., 1998) and a definition proposed by Lea Steele on the basis of her work with Gulf War veterans in Kansas (Steele, 2000) (see Table 4-2). Other definitions include the Gulf War illness syndromes proposed by Robert Haley and colleagues based on factor analysis and clinical assessments (Haley et al., 1997b); three categories of symptoms identified in veterans living near Portland, Oregon (Bourdette et al., 2001; Spencer et al., 1998); and symptom reporting by veterans in the National Health Survey of Gulf War Veterans and Their Families begun by VA in 1995 (Kang et al., 2000, 2009). This multiplicity of definitions makes it difficult to compare results across studies of Gulf War illness.

Prior IOM committees and other organizations have struggled with choosing a name or label to exactly delineate the complex set of symptoms that Gulf War veterans present with. A variety of terms have been used to refer to what was initially labelled "Gulf War illness," and this proliferation of definitions has resulted in a lack of clarity and inconsistency in the research literature as to what symptoms or conditions are actually being studied. The VA has traditionally used the term "unexplained illnesses" for the symptoms experienced by Gulf War veterans. "Gulf War syndrome" was used shortly after the war, but in general most groups, including the RAC, have used the term "Gulf War illness," although there is no ICD code for such an array of symptoms. The Volume 4 committee approached the issue of multisymptom illnesses from the perspective of "unexplained illness," focusing on symptoms reported by Gulf War deployed veterans in efforts to determine whether the presenting symptoms defined a unique illness complex. The Volume 8 committee did not attempt to make such a determination, but rather accepted that "multisymptom illness" was in itself a diagnostic entity and assessed the literature regarding the association between symptom reporting indicative of "multisymptom illness" and deployment to the Gulf War.

Recently, the IOM report *Chronic Multisymptom Illness in Gulf War Veterans: Case Definitions Reexamined* (IOM, 2014a) reconsidered chronic multisymptom illness in Gulf War veterans. After carefully examining the existing definitions (Haley et al., 1997b; Fukuda et al., 1998; Steele, 2000; Bourdette et al., 2001; Spencer et al., 1998; Kang et al., 2009) that committee concluded that two of those definitions—the CDC and the Kansas definitions—appeared to capture the most salient and commonly identified arrays of symptoms presented by

deployed veterans, although neither definition captured all aspects of a case definition. All of the studies reviewed by that committee included reports of fatigue, pain, and neurocognitive symptoms. The committee recommended that VA use those two case definitions, pointing out that each of the definitions could serve specific needs. The CDC definition was considered to be less suitable for research that would require a more narrowly defined study population; whereas, the Kansas definition, which is more rigorous, might identify too few cases, thus, compromising the needed statistical power for studying various outcomes of interest. From a practical perspective, adapting the definitions for use in clinical settings was another priority.

TABLE 4-2 Case Definitions of Gulf War Illness* Used in Gulf War Veteran Studies

Definition	Symptoms
CDC (Fukuda et al., 1998)	One or more from at least two of the following categories: 1. Fatigue 2. Mood and cognition (symptoms of feeling depressed, difficulty in remembering or concentrating, feeling moody, feeling anxious, trouble in finding words, or difficulty in sleeping) 3. Musculoskeletal (symptoms of joint pain, joint stiffness, or muscle pain) Duration: ≥ 6 months; severity: mild, moderate, or severe by self-report
Kansas (Steele, 2000)	Three of six domains: 1. Fatigue and sleep problems 2. Pain symptoms 3. Neurologic, cognitive, or mood symptoms 4. Gastrointestinal symptoms 5. Respiratory symptoms 6. Skin symptoms Exclusions: Symptom reporting must be in the absence of diagnosed exclusionary conditions; only respondents who have at least one moderately severe symptom or two or more symptoms within a group were considered to have a high level of symptoms in the group Duration: chronic; onset: since 1990; severity: mild, moderate, or severe by self-report
Haley (Haley et al., 1997b)	Cases are defined mathematically by using factor scores calculated with weights; cases with factor scores > 1.5 are identified as having a syndrome (a factor derived with the same factor analysis); cases may have multiple syndromes. Three major syndromes: 1. Impaired cognition characterized by problems with attention, memory, and reasoning, as well as insomnia, depression, daytime sleepiness, and headaches 2. Confusion-ataxia characterized by problems with thinking, disorientation, balance disturbances, vertigo, and impotence 3. Arthromyoneuropathy characterized by joint and muscle pains, muscle fatigue, difficulty lifting, and extremity paresthesias

* Gulf War illness is called chronic multisymptom illness in the IOM report.
SOURCE: Adapted from IOM (2014a).

Besides recommending that VA use both definitions, the committee also recommended that VA systematically monitor data to identify and further refine additional features of chronic multisymptom illness, such as onset, duration, severity, frequency of symptoms, and exclusionary criteria in order to produce a more robust case definition. The committee also recommended that VA use the term "Gulf War illness" rather than "chronic multisymptom

illness" for symptomatic Gulf War veterans. The Volume 10 committee uses the term "Gulf War illness" in its discussion of this constellation of symptoms but uses the terms cited by a study's authors in summaries of the studies.

Summary of Volumes 4 and 8

The Volume 4 committee noted that findings from factor and cluster analyses for symptoms of Gulf War illness (the committee used the term "unexplained illness") seem quite similar despite methodologic differences. Similar symptom clusters include neurocognitive symptoms, musculoskeletal symptoms, and peripheral nervous system symptoms. Less commonly reported are symptom clusters involving gastrointestinal and respiratory symptoms. Among the five primary studies of veterans from Iowa (Doebbling et al., 2000), Australia (Forbes et al., 2004), two UK cohorts (Cherry et al., 2001a; Ismail et al., 1999), and a large national cohort studied by VA (Kang et al., 2002), factor analysis started with representative, generalizable populations and high participation rates. These primary studies found that in general deployed veterans reported more symptoms or more severe symptoms than their nondeployed counterparts. There were seven secondary studies (Fukuda et al., 1998; Knoke et al., 2000; Haley et al., 1997b, 2001; Bourdette et al., 2001; Shapiro et al., 2002; Hallman et al., 2003) that fell short on either the criteria of having high participation rates or having representative samples, that is, the studies included members of only one branch of the service, had small samples of veterans, or used only symptomatic groups of veterans, thus lacking a nonsymptomatic comparison group. Nevertheless, the results of the secondary studies are valuable and add detail to the epidemiologic literature on Gulf War veterans. Although the committee did not find a unique syndrome, illness, or symptom complex in deployed Gulf War veterans, it did report that Gulf War veterans had higher rates of nearly all symptoms or sets of symptoms than their nondeployed counterparts.

The Volume 8 committee considered new information on factor analyses and cluster analyses. That committee found no new studies using factor or cluster analyses on veterans with symptoms of Gulf War illness and discussed only one new primary study focused on prevalence of chronic multisymptom illness (Blanchard et al., 2006). The large and nationally representative National Health Survey of Gulf War Era Veterans and Their Families conducted by VA in 1993–1995, found that nearly 30% of deployed veterans met the CDC case definition of "multisymptom illness" compared with 16% of nondeployed veterans. The Volume 8 committee agreed with the Volume 4 committee in that there was increased reporting of symptoms indicative of multisymptom illness among those deployed to the Gulf War. Furthermore, this increased symptom reporting was also found for deployed veterans from several coalition countries including the UK, Australia, Canada, and Denmark, thus adding credence to the findings. The findings across all the studies considered in Volume 8 were similar, broadly describing neurologic, psychologic, cognitive, fatigue, and musculoskeletal symptoms. Even though some studies that compared the most representative samples found symptom patterns that were similar between the deployed and nondeployed groups, symptoms were more severe or more frequent in the deployed than in the nondeployed groups. *The Volume 8 committee concluded that there was sufficient evidence of association between deployment to Gulf War and chronic multisymptom illness.*

New Literature

This committee reviewed epidemiologic, clinical, and physiologic studies related to Gulf War illness. A major limitation with many of these studies, in particular the epidemiologic ones, is the use of retrospective information (recalled exposures) not clearly verifiable as well as the length of time that has elapsed since the original exposure—that is, deployment to the Persian Gulf region—and the numerous voluntary and involuntary exposures to environmental and other agents that the veterans may have experienced since deployment. In a comparison of symptoms reported by U.S. and UK troops in earlier surveys, Ismail et al. (2011) found that deployed troops from both countries reported more symptoms than nondeployed troops from either country. The most frequently reported symptoms were similar across all four groups (that is, unrefreshed sleep, headaches, irritability, fatigue, and pain).

The Volume 10 committee identified two primary studies and one secondary study that provided new information on Gulf War illness published after the Volume 8 report**.**

Primary Study

In 2000–2002, Kelsall et al. (2009) conducted a longitudinal assessment of 1,381 of the 1,871 eligible Australian male veterans who had deployed to the Gulf War and a comparison group of 1,085 veterans who had been on active service during the war but had not deployed, as well as 292 veterans who had deployed elsewhere during the war. All the veterans completed a 63-item symptom questionnaire, as well as the 12-item General Health Questionnaire (a measure of psychological distress), the 12-item Short-Form Health Survey (a measure of health-related quality of life), and the Alcohol Use Disorders Identification Test (AUDIT). Veterans also received an in-person health assessment that included a full physical examination, with lung function and fitness tests, and a mental health assessment using the psychologist-administered, computer-assisted Composite International Diagnostic Interview (CIDI). Multisymptom illness was defined using a modification of the CDC operational definition that required one or more symptoms in the past month rated as at least of moderate severity from at least three of four categories (fatigue, "psycho-physiological," cognitive, and arthroneuromuscular).

The prevalence of multisymptom illness was 25.6% in the Gulf War veterans and 16.0% in the total comparison group. The excess risk of having multisymptom illness in the deployed veterans was statistically significant (OR = 1.80, 95% CI 1.48–2.19); models were adjusted for age, military service, rank, education, marital status, other medical conditions, AUDIT score, smoking, health, weight, atopy, and history of diabetes. The odds ratio of multisymptom illness was greatest when deployed veterans were compared with veterans who had not deployed at all (OR = 1.91, 95% CI 1.55–2.36) versus veterans who had deployed elsewhere (OR = 1.45, 95% CI 1.03–2.04). Multisymptom illness was associated with functional and occupational impairment, increased health care utilization, unexplained chronic fatigue, slightly elevated neuropathy score, and increased waist circumference, but not with reduced spirometry performance, lung function, or elevated blood pressure. In particular, multisymptom illness was strongly associated with affective disorder, major depression, any anxiety disorder (but not posttraumatic stress disorder [PTSD]), somatoform disorder, and alcohol use or dependence disorder, in the Gulf War deployed and nondeployed veterans but not in the deployed elsewhere comparison group (Kelsall et al., 2009).

Laboratory values for Gulf War veterans with multisymptom illness were significantly elevated for inflammation (erythrocyte sedimentation rate > 10 mm/hour or > 15 mm/hour if >

50 years of age; C-reactive protein > 10 mg/L or leukocyte count > 11.0 x 10^9/L) and elevated random plasma glucose compared with deployed veterans who did not have multisymptom illness. Deployed elsewhere veterans with multisymptom illness also showed an elevated plasma glucose compared with their healthy counterparts; these veterans also had more markers of liver disease as determined by alanine aminotransferase > 55 U/L and aspartate aminotransferase > 45 U/L (OR = 6.20, 95% CI 1.61–23.93; adjusted for military service, age, rank, education, and marital status). Nondeployed veterans with multisymptom illness had more markers of obstructive liver disease than their counterparts without multisymptom illness. There were no other significant differences in laboratory values between veteran groups with multisymptom illness and those without it (Kelsall et al., 2009).

In a follow-up to Kelsall et al. (2009), Sim et al. (2015) reported on the Australian Gulf War Veterans' Follow-Up Health Study, conducted between 2011 and 2013. This study is an assessment of the entire 1,871 Australian Gulf War cohort, 10 years after the 2000–2002 baseline study (Kelsall et al., 2006) and 20 years after the war. Because only about 2% of the participants were women, only results pertaining to males were reported. Results were adjusted for age, rank category, and service branch. Of the 1,456 eligible deployed veterans, 715 participated in the study and 675 of the 1,449 nondeployed veterans provided the comparison group. As with the earlier study, veterans completed a 63-item general health symptom questionnaire (sent via mail) and an over-the-phone CIDI, and gave consent for their Department of Defence health records and Medicare claims to be accessed. In-person health assessment or physical examinations were not performed. Gulf War deployed veterans reported a greater prevalence of all 63 symptoms and the difference was statistically significant for 47 of them. Results showed a greater increase in the number of symptoms reported for deployed versus nondeployed veteran. Among the 20 most prevalent symptoms, half were significantly more persistent and/or more incident in the deployed group. The follow-up survey used the same criteria for multisymptom illness as the 2000–2002 baseline study. The prevalence in Gulf War veterans was 29% in veterans who met the criteria for multisymptom illness compared with 18% in nondeployed veterans (these percentages dropped to 26% and 16%, respectively when cases with explanatory conditions were excluded). Gulf War veterans were significantly more likely to have multisymptom illness at follow-up (OR = 1.60, 95% CI 1.31–1.95) than their nondeployed counterparts.

Secondary Study

The wave 3 survey of the cross-sectional National Health Study of Persian Gulf War Era Veterans (discussed in greater detail in Chapter 3), conducted in 2012–2013 via mail, website, or a computer-assisted telephone interview, asked 8,104 deployed and 6,148 Gulf War era veterans to indicate whether they had experienced a number of physical and mental health symptoms (Dursa et al., 2016). The survey also asked veterans about the presence and occurrence of any unexplained multisymptom illnesses. The weighted prevalence of reporting of multisymptom illness increased from just over 36% in 2005 to 43.9% in 2013 for deployed veterans and from about 12% in 2005 to 20.3% in 2013 for era veterans (Dursa et al., 2016; Kang et al., 2009). There was a significant difference in the prevalence of chronic multisymptom illness between deployed and era veterans (OR = 3.06, 95% CI 2.78–3.83). The OR was adjusted for age, race, sex, body mass index (BMI), smoking status, service branch, and unit component. The presentation by VA on the preliminary results of this survey noted that among deployed and era veterans with self-reported lifetime chronic multisymptom illness, there was a statistically

significant difference in symptom reporting in the past 12 months only for unrefreshing sleep, headaches, and trouble finding words (Bossarte, 2014).

Other Related Studies

Since publication of Volume 8, there have been several new studies focusing on the association of Gulf War illness symptoms with potential exposures and biological mechanisms that may be responsible for the symptoms. During its review of the published literature, the committee identified studies on Gulf War illness that, while they did not meet the criteria for being considered as primary or secondary studies, provided information that the committee believes may be useful in addressing future research questions related to Gulf War illness. The studies focus on three main areas: the effect of Gulf War illness on other health conditions and vice versa; new efforts to link Gulf War illness with particular exposures prior to or during deployment, and neuroimaging and brain metabolism studies that attempt to identify biomarkers of Gulf War illness in brain or other tissues. Investigators for these studies used a variety of definitions of Gulf War illness (or chronic multisymptom illness), including the CDC definition (Fukuda et al, 1998), the Kansas definition (Steele, 2000), and Haley's Gulf War illness syndromes (defined by 3-6 symptom clusters) (Haley et al., 1997b).

VA provided a health care use report for Gulf War deployed and era veterans who sought care in VA facilities from October 2001 to December 2013. The report presented the prevalence of diagnoses of diseases by ICD-9 code categories; no statistical testing was performed. 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. A total of 286,995 Gulf War deployed and 296,635 era veterans received treatment at VA over the approximately 11-year period. These VA health care users represent 46% of all deployed Gulf War veterans and 36% of all nondeployed era veterans. Of these users, 176,541 (61.5%) of the deployed Gulf War veterans and 157,051 (58.2%) of the nondeployed veterans presented with symptoms, signs, and ill-defined conditions (ICD-9-CM 780-799). The most commonly reported of these were general symptoms (> 50% of veterans in both groups reported having them), respiratory (> 39%), and skin (> 26%) (VA, 2014a,b).

Comorbidities

Gulf War illness is not only characterized by a broad range of symptoms, but it has also been associated with other more clearly defined health conditions. Several researchers have attempted to determine whether having Gulf War illness puts a veteran at risk for developing another disease or whether having any particular medical diagnosis or symptoms makes a veteran more susceptible to having Gulf War illness. In this section, the committee considers some of the recent literature on Gulf War illness and its possible comorbidities.

Wallin et al. (2009) assessed neuropsychologic performance in Gulf War deployed veterans with Gulf War illness (n = 25) and without (n = 16), obtained from the 1995 population-based National Health Survey of Gulf War Era Veterans and Their Families. Cases were defined as meeting the CDC criteria for Gulf War illness. The neuropsychological testing battery included assessment of verbal abilities, attention, memory and learning, problem solving, and motor skills. There were no significant differences between cases and controls for any of the cognitive domains, and the composite test scores for both groups were within normal limits. However, there were statistically significant differences in Personality Assessment Inventory scores used to assess psychiatric symptoms; cases were significantly more impaired than controls on 8 of 11 clinical scales such as somatic complaints, anxiety, depression, mania, and paranoia.

Responses to the SF-36 indicated that cases also had poorer self-reported general physical and mental health.

Two new studies have assessed autonomic dysfunction in veterans who have Gulf War illness. In a nested case-control study, Haley et al. (2013) used the Autonomic Symptom Profile questionnaire (a self-administered questionnaire), the Composite Autonomic Severity score, and high-frequency heart rate variability data from a 24-hour electrocardiogram to assess whether some of the symptoms of Gulf War illness are due to autonomic dysfunction. Veterans were selected from the U.S. Military Health Survey (Iannachionne et al., 2011). Sixty-six veterans met Haley's definitions for one of three syndromes of Gulf War illness (21 with syndrome 1, 24 with syndrome 2, and 21 with syndrome 3), 16 veterans were not ill and had deployed to the Kuwaiti theater during the war, and 15 veterans were in the military but did not deploy. All veterans with Gulf War illness reported significantly more autonomic symptoms ($p < 0.001$) and had elevated Composite Autonomic Symptom Scale scores (scores were most elevated for syndrome 2 primarily due to a reduction in sudomotor function in the foot), compared with controls. Ill veterans also lacked the normal increase in high-frequency heart rate variability at night compared with controls.

In the second study, Li et al. (2014) also studied autonomic dysfunction in 16 veterans with Gulf War illness and 12 era controls. Ill veterans were those who self-reported chronic fatigue syndrome-like multisymptoms in the 2005 survey titled "Health of U.S. Veterans of 1991 Gulf War: A Follow-up Survey in 10 Years." Veterans responded to autonomic nervous system questionnaires and received physical examinations, including large fiber nerve conduction studies, quantitative sensory testing, autonomic testing, a quantitative sudomotor axon reflex test, and a diagnostic tilt-table test. Five veterans in the ill group had impaired cardiovascular function, whereas none of the control group had any impairment. The ill group also had significantly higher baseline heart rate and higher scores on a compound autonomic scoring scale compared with controls. The authors suggest that objective autonomic testing should be carried out on veterans with Gulf War illness who complain of unexplained postexertional fatigue.

In a 2003–2005 follow-up to the 1995 National Health Survey of Gulf War Veterans and Their Families, Coughlin et al. (2011b) assessed alcohol consumption in 9,970 respondents and found that veterans who were problem drinkers (defined as answering yes to any of five questions about problem drinking or hazardous driving in the past 6 months) were more likely to have unexplained multisymptom illness (defined as having unexplained physical symptoms and illnesses that persisted for 6 months or longer and were not explained by other diagnoses) with an odds ratio of 1.56 (95% CI 1.37–1.77, $p < 0.001$), adjusted for age, sex, race/ethnicity, branch of service, rank, and deployment status. These authors used the same survey results to assess the association between body-mass index (BMI) and various health conditions. Multisymptom illness was more prevalent in Gulf War deployed veterans who were obese than in normal weight deployed veterans, but this increase was not evident in a multivariate analysis (Coughlin, 2011a).

Many veterans with Gulf War illness report problems with sleep. In a small study of 18 male veterans with Gulf War illness and 11 asymptomatic control veterans, Amin et al. (2011) found that veterans with the illness had a statistically significant increase in the frequency of sleep arousals from apneas or hypoapneas ($p = 0.006$), and flow-limited breaths ($p < 0.0001$); differences in other sleep parameters were not significant between the two groups. The samples were matched for age and BMI. Compared with 36% of control veterans, 96% of veterans with Gulf War illness had their breathing flow limited.

Many veterans with Gulf War illness complain of having headaches. Rayhan et al. (2013b) examined the presence of headache that accompanied Gulf War illness in a small study of 50 veterans with the illness based on the CDC definition (Fukuda et al., 1998), 39 subjects with chronic fatigue syndrome (CFS) based on the 1994 CDC criteria, and 45 control subjects (veteran status was not reported for the latter two groups). Compared with 13% of controls, migraines were endorsed in 64% of the veterans with Gulf War illness (OR = 22.5, 95% CI 7.8–64.8). Migraines were frequently comorbid with tension headaches (20 of 32 veterans: OR not reported); tension headaches without migraines occurred in about 20% of the veterans with Gulf War illness and 26% of the controls. Most of the migraines associated with Gulf War illness were with aura (24 of 32); only 8 of 32 did not have aura.

Deployment Exposures and Gulf War Illness

Steele et al. (2012) conducted a case-control study in 2000 that compared Gulf War veteran's exposures in a population-based sample of 304 deployed veterans, 144 with Gulf War illness and 160 healthy controls. Case status was determined based on screening using the CDC definition, and subsequent inclusion in the study was based on the Kansas definition for Gulf War illness. Study participants were asked about their deployment locations and duration and whether they had any of 19 specific exposures or experiences during deployment. Among veterans in Iraq or Kuwait, Gulf War illness was most strongly associated with the use of pyridostigmine bromide (PB) tablets (OR = 3.5, 95% CI 1.7–7.4), being within 1 mile of an exploding Scud missile (OR = 3.1, 95% CI 1.5–6.1), using pesticides on the skin (OR = 2.07, 95% CI 1.06–4.05, and being exposed to smoke from oil-well fires (OR = 2.78, 95% CI 1.01–7.66). For veterans who were in support areas, Gulf War illness was most closely associated with wearing pesticide-treated uniforms (OR = 12.7, 95% CI 2.6–61.5). For all veterans combined, Gulf War illness was also significantly associated with frequently getting less than 4 hours sleep in 24 hours (OR = 2.91, 1.41–6.01).

Haley and colleagues have published a number of studies looking at the epidemiology of the syndromes they have elicited from veterans, as well as using purposive subsamples of subjects meeting criteria for the various syndromes, and performing mechanistic and etiologic experiments in efforts to identify the underlying pathophysiology for each of the three primary Gulf War illness syndrome variants Haley et al. have defined. The publications of this research group have been criticized for restricting their subjects to a pool of 249 out of 606 original veterans of the Twenty-Fourth Reserve Naval Mobile Construction Battalion (Seabees), thus making it difficult to generalize the findings to the entire Gulf War veteran cohort. In a recent publication, Iannacchione et al. (2011) conducted a validation study among a stratified random sample of over 8,000 deployed and deployable-but-nondeployed veterans selected from all Gulf War active duty and ready reserve veterans. Termed the U.S. Military Health Survey, this study was conducted by telephone between May 2007 and April 2009; the response rate was 60%. Iannacchione et al. report validating, through factor analysis and related techniques, their original three major and three minor Gulf War illness syndromes. The authors also collected information on whether veterans in the validation study met the CDC's criteria for multisymptom illness, but these data were not reported. Results from the survey indicated that the overall case definition of Gulf War illness was more prevalent in the deployed than nondeployed veterans (OR = 3.87, 95% CI 2.61–5.74); veterans were considered to have met the overall factor case definition if they met any of the six dichotomized component definitions. Each of the Gulf War illness variants was also more prevalent in the deployed veterans than the nondeployed veterans (OR =

3.33, 95% CI 1.10–10.10, for syndrome variant 1; OR = 5.11, 95% CI 2.43–10.75, for variant 2; and OR = 4.25, 95% CI 2.33–7.74, for variant 3).

Haley and Tuite (2013) examined the relationship between the cohort identified in Iannacchione et al. (2011), the prevalence of Gulf War illness (based on both the CDC and the factor analysis case definitions), and the two dependent variables of chemical alarm awareness and unit location with respect to the Khamisiyah explosions. They estimated that 13.6% of the veterans deployed to the Kuwaiti theater of operations had Gulf War illness using the factor-analysis case definition, whereas 41.7% had it on the basis of the CDC definition (95% of veterans classified as having Gulf War illness by the factor analysis met the CDC case definition as well). It was further estimated that 39% of veterans in the theater had exposure to low levels of nerve agents based on responses to the survey question about hearing chemical alarms, and 16% may have been located in the plume of nerve agent from the Khamisiyah demolition based on Department of Defense (DoD) exposure models. The risk of having Gulf War illness (Haley overall factor case definition) was strongly associated with hearing chemical alarms (OR = 4.13, 95% CI 2.51–6.80), and the authors found a dose–response relationship between the relative risk of having Gulf War illness and the number of alarms heard. The risk of Gulf War illness and being in the nerve agent plume was not statistically significant (OR = 1.21, 95% CI 0.86–1.69). The authors suggest that factor analysis syndrome 1 is less likely to be related to nerve agent exposure than the other two major syndromes. A strong role for recall bias to produce the relationships with recalled chemical alarms cannot be excluded (the survey was conducted from 2007 to 2010). The two epidemiologic studies by Haley and colleagues do not appear to shed much light on the etiology or mechanism of Gulf War illness, however, they do advance the stature of the factor analysis case definitions of the illness into apparently representative national samples.

The committee recognizes that association is not causation, but felt it was important to look for consistency of associations across studies. One study reports that exposures for which there were significant associations with Gulf War illness include self-reported PB use, proximity to Scud missile explosions, pesticides on skin, wearing permethrin-treated uniforms, and smoke from oil-well fires (Steele et al., 2015), whereas the studies by Haley and Tuite (2013) and Iannacchione et al. (2011) indicated that hearing chemical alarms—but not the nerve agent plume—was associated with the development of Gulf War illness. Together these studies suggest the possibility that chemical exposures—PB, pesticides, insecticide treatment, and alarms—may play a role in Gulf War illness. Nevertheless, the committee cautions that a substantial limitation to this potential association is the lack of any measure that clearly documents the actual chemicals or doses to which the veterans were exposed. Gulf War veterans from the coalition forces also reported increased symptoms indicative of Gulf War illness, but their exposures were may have differed from those of U.S. service members. For example, Danish troops were in the Persian Gulf region after the war as peacekeepers and were not exposed to sarin (Ishoy et al., 1999b). There are no reliable or validated biomarkers to indicate that a particular veteran with or without Gulf War illness had a specific chemical exposure during deployment. Also, there is little biologic plausibility for the concept that exposure to PB concentrations that did not cause acute effects would result in long-term effects (IOM, 2004). The committee concludes that, on the basis of the studies of deployment exposures and Gulf War illness (e.g., Steele et al., 2015; Haley and Tuite, 2013; Iannacchione et al., 2011), there is little new information that sheds light on the etiology of or mechanisms for Gulf War illness.

Genetic Factors and Gulf War Illness

There is considerable evidence that a set of genes that is important in metabolizing toxicants is involved in the development of some diseases such as amyotrophic lateral sclerosis (ALS). To explore the etiology of Gulf War illness, several researchers have sought to identify genetic mutations that would affect the body's ability to metabolize certain toxicants associated with Gulf War deployment, with a particular focus on genes that encode proteins that metabolize cholinesterase inhibitors. PB, some pesticides, and sarin and cyclosarin are potentially toxic exposures that are known to inhibit cholinesterase. Without cholinesterase to inactivate acetylcholine (a neurotransmitter), overstimulation of organs and muscles controlled by acetylcholine may occur.

The most relevant proteins are paraoxonases[8] (PON) 1, 2 and 3; butyrylcholinesterase[9] (BChE); acetylcholinesterase (AChE); and cytochrome P450-2D6 (CYP2D6). PON and BChE have received the most study in Gulf War illness and so are reviewed here briefly.

The Voluem 10 committee reviewed studies described in Volume 8 as well as new studies of genetic associations to interpret the evidence as a whole. The Volume 8 committee reviewed several studies that sought to positively link PON1 genotype (Haley et al, 1999; Mackness et al., 2000; Hotopf et al., 2003b) or BChE genotypes (Lockridge, 1999; Sastre and Cook, 2004) to Gulf War illness; these were generally underpowered and inconsistent. The Volume 8 committee recommended that well-designed studies be undertaken and replicated to robustly test the hypothesis that variants in genes that code for detoxifying enzymes for cholinesterase inhibitors may be a susceptibility factor for development of Gulf War illness.

As described in Volume 8, a genetic association between cholinesterase inhibitors and PON1 was first proposed by Haley et al. (1999) who studied 25 symptomatic Gulf War veterans. The authors suggested that PON1 variants are overrepresented in Gulf War illness; however, this study did not reach statistical significance ($p = 0.08$ before correction for multiple comparisons). Mackness et al. (2000) initially reported an association of Gulf War illness with reduced PON1 enzyme activity; however, Hotopf et al. (2003b) reported that PON1 levels are low in both symptomatic and asymptomatic Gulf War veterans.

Lockridge et al. (1999) reported that rare, low-activity variants of BChE are overrepresented in symptomatic Gulf War veterans, but Sastre and Cook (2004) could not replicate this. They found an association between multisymptom illness and carriers of rare

[8] The paraoxonases (PON) 1, 2 and 3 are esterases, encoded by genes on chromosome 7, which metabolize oxidized lipids as well as a range of cholinesterase inhibitors (sarin, soman, diazinon, chlorphyrifos). They also oxidize some clinically approved compounds, such as the statins. PON1 has upwards of 200 genetic variants in normal individuals. The most common are the variants glutamine-192-arginine and leucine-55-methionine. Also of interest are two regulatory polymorphisms within the PON1 promoter. The impact of these variants on PON1 hydrolase activity varies with the substrate. For example, at codon 192, variant Q has higher activity for sarin, soman, and diazinon, while variant R has higher activity for parathion and paraxon. Studies of the C-108T promoter polymorphism show that the C allele has higher promoter activity (Brophy et al., 2001; Costa et al., 2005; Davies et al, 1996, Vol 8).

[9] BChE (pseudocholinesterase, plasma cholinesterase, chromosome 3q) hydrolyzes many choline esters, including butyrylcholine, a synthetic substance. BChE inactivates organophosphates by both binding and hydrolyzing them. BChE has been studied extensively because of its role in metabolizing succinylcholine. There are several allelic variants in the BChE gene, identified as BChE-U, which has high enzyme activity, and allelic vairants K, A, and F, which are less common and have less activity. The lower activity alleles are sometimes lumped in one category (Jensen et al., 1995).

BChE genotypes who also self-reported PB exposure. A caveat is that the numbers of carriers of rare genotype were small in these studies (11/226 in Lockridge; 28/304 in Sastre and Cook).

Four new studies investigating the role of certain genes in Gulf War illness were identified and reviewed by the Volume 10 committee (Steele et al., 2015; Georgopoulos et al., 2015; Haley et al., 2010; Craddock et al. 2015). Steele et al. (2015) examined Gulf War illness (using Kansas and CDC definitions) in relation to BChE activity and genotype, and examined deployment exposures to pesticides and PB use in 144 Gulf War veterans with symptoms of the illness and 160 asymptomatic veterans. While cases and controls did not differ by BChE activity or genotype, BChE activity did differ by genotype. The 276 veterans with the more common genotypes (designated BChE-U; including U/U and U/K genotypes) had significantly higher BChE activity than the 28 veterans with the less common variants (designated BChE-LCV; including K/K, U/AK, U/A, A/F, and AK/F genotypes). There were no differences between veterans with and without Gulf War illness in regard to associations between BChE activity (low versus high activity measured by benzocholine in serum) and self-reported exposures to PB and pesticides. However, when the veterans were stratified by BChE genotype (BChE-U versus BChE-LCV), those who reported taking PB pills were more likely to have Gulf War illness than those who did not (OR = 40.00, $p = 0.0005$). The same association existed for the BChE-U group, but the magnitude of the association was less (OR = 2.68, $p = 0.0001$). The difference between those two associations was significant ($p = 0.019$), thus the authors suggest an interaction between BChE genotype and PB that affects the risk of Gulf War illness such that Gulf War veterans who have BChE-LCV genotypes and took PB are at greatest risk comparatively in this study. The committee notes that the number of cases in these groups were small; there were only 28 veterans in the BChE-LCV group—14 with Gulf War illness (of whom 13 had PB exposure) and 14 without (of whom only 3 had PB exposure). By contrast, members of the BCHE-LCV group did not have a higher risk of Gulf War illness if they reported chemical weapons exposure. Lastly, when the authors re-sorted the cases not using the CDC case definition for Gulf War illness (a broader definition than the Kansas definition), the result was the same but less pronounced.

Another analysis suggests that in veterans with Gulf War illness, altered immune function may be related to human leukocyte antigen (HLA) genes (Georgopoulos et al., 2015). Like Steele et al. (2015), this investigation used a sample of Gulf War veterans (66 with Gulf War illness, using either the CDC criteria or the Kansas case definition, and 16 without the illness) who had participated in the earlier study described in Steele (2000). Nine HLA genes were compared between the two groups and 144 unique alleles of Class I and II HLA genes were found. Six Class 11 alleles were found to correctly classify veterans as either cases or controls 84% of the time (sensitivity = 84.8%; specificity = 81.2%) and results were statistically significant. The frequency of the six alleles appeared to be protective in the control group such that allele frequencies were significantly lower among cases ($p<0.002$) and there was a negative correlation between overall symptom severity and frequency of the six alleles ($p<0.0001$). Two of the six alleles were completely absent among veterans with Gulf War illness. The authors interpret their findings as indicating that veterans with Gulf War illness might have a genetic susceptibility by which certain exposures (possibly vaccination or chemical exposures) result in immune dysfunction and the symptoms of Gulf War illness.

In a subset of Gulf War veterans, Haley et al. (2010) further analyzed levels of Q192 versus R192 serum PON1 activities and investigated the relationship between enzyme activity, the PON1 Q192R genotype, and exposure to nerve agents. Using a history of an alarm sounding

as a marker for early exposure to these agents, the authors concluded that early exposure was strongly associated with Gulf War illness, and the risk was highest in individuals with the lowest quartile of Q-isozyme activity.

Craddock et al. (2015) examined the association between gene expression patterns in male veterans with Gulf War illness to gene expression patterns associated with some human conditions and to genes targeted by known pharmaceuticals. The study collected data and specimens from 17 veterans with Gulf War illness (using the CDC case definition) and 22 healthy but sedentary Gulf War era veterans between 2006 and 2008. Nineteen gene expression patterns were significantly associated with Gulf War illness; these patterns were correlated to 18 conditions that share features of Gulf War illness.[10] Eight of the 19 modules of genes associated with Gulf War illness had known drug targets. Rheumatoid arthritis was found to be correlated with the same eight modules. The authors interpreted their work to support previous studies that suggested that Gulf War illness is associated with dysregulation in some genetic pathway and to hypothesize potentially useful drug treatments.

Immune Function and Cytokines in Gulf War Illness

Eight studies examined immune function and cytokines in veterans with Gulf War illness. Five are from one group that tested the hypothesis that Gulf War illness involves a dysfunction in the immune system. One looked for abnormal patterns of pro-inflammatory immune markers, one study reported a comparison of cytokine expression in patients with either Gulf War illness or myalgic encephalomyelitis, and the final study looked at immune function in veterans with Gulf War illness. Each is discussed below.

Five papers on the immune system (Broderick et al., 2011, 2012, 2013; Smylie et al., 2013; Whistler et al., 2009) all used a similar exercise protocol to stimulate the immune system and tested responses. The initial pilot study (Whistler et al., 2009) tested the hypothesis that physiological responses to stress might differ in veterans with Gulf War illness. Nine veterans with Gulf War illness and 11 sedentary, nondeployed veterans were tested for stress-related biomarkers before, during, and after a standard bicycle ergometer exercise test. Endpoints measured included blood cell counts, natural killer (NK)-cell cytotoxicity, cytokines, expression levels of 20,000 genes, and salivary cortisol. As expected, exercise increased blood lymphocyte levels in the controls, but this response was muted in veterans with Gulf War illness. Compared with control veterans, Gulf War illness veterans had the following: decreased NK-cell cytotoxicity, altered gene expression associated with NK-cell function, decreased blood concentrations of pro-inflammatory cytokines, T-cell ratios (CD4/CD8), and mediators of the stress response, including decreased salivary cortisol. The authors concluded that Gulf War illness involved impaired immune function. The authors suggested an overlap in symptomology and clinical findings with persons who have CFS.

A later study published by the same group (Broderick et al., 2011) appears to be from the same cohort and with similar samples as reported by Whistler et al. (2009), but the samples are analyzed in a different way. Instead of making comparisons between individual cytokines, the authors used multivariate statistical models to determine patterns of change shared by various

[10] In order from most correlated to least correlated: frontotemporal lobar degeneration (FTLD) sporadic frontal; cerebral palsy semitendinous muscle; schizophrenia; FTLD progranulin mutation frontal; benzene exposure; autism; bipolar disorder; chronic stress; adenocarcinoma of the esophagus; acute quadriplegic myopathy; spastic paraplegia; mixed hyperlipidemia; glaucoma; nonsevere asthma CD8 T-cells; multiple sclerosis; Crohn's disease; Becker muscular dystrophy; and sickle cell disease.

cytokines, cortisol, and neuropeptide Y, to analyze the "fight or flight" response to exercise. The method used a form of graph theoretical methods and complex mathematical systems to identify significant trends shared by pairs of biomarkers and then constructed association networks linking immune and endocrine biomarkers in each study group (see Broderick et al., 2011, for details). The results reported differ from those reported by Whistler et al. (2009), but the authors mention several times that their method of analysis can detect altered patterns in the immune system that would not be detected by standard analyses. The authors concluded that the study showed that "the potential heightened lymphocyte and hypothalamic-pituitary-adrenal axis (HPA) responsiveness to IL-1 stimulation in the context of a mixed Th1:Th2 immune signature supports an autoimmune component to Gulf War illness."

In Broderick et al. (2012), the authors sought to determine if the expression of immune biomarkers can be used to diagnose Gulf War illness. The results indicate that such biomarkers are not adequate for the diagnosis of Gulf War illness in individuals, but they could offer insight into the physiological basis for the disease. In a later paper (Broderick et al., 2013), the same protocol was used to test the difference in immune response to exercise in patients with Gulf War illness (n = 20) compared with those with CFS/myalgic encephalomyelitis (CFS/ME) (n = 7) and with healthy veterans (n = 22). Earlier studies (Barbier et al., 2009) had indicated that gene expression in stressed mice exposed to PB showed increases in hippocampal expression of three genes involved in memory development: brain-derived neurotrophic factor, tropomyosin-related kinase B, and calcium/calmodulin protein kinase II alpha. These studies could not be conducted in humans, but the investigators used circulating lymphocytes to reflect changes in the brains of veterans. The hypothesis was the NF-kappa beta activity was altered in circulating lymphocytes of Gulf War illness subjects as a lasting result of exposure to acetylcholinesterase inhibitors in the field. The authors performed an analysis of gene expression using a novel methodology (Efroni et al., 2007, 2008) for estimating the activity level of over 400 pathways described in National Cancer Institute databases. The authors point out that this is a significant departure from conventional analysis, where no estimate of pathway activation is produced. Using the alternative approach, pathway activation from gene expression in peripheral blood monocytes before, during, and after exercise in Gulf War illness and in healthy veterans was estimated. A statistical association of baseline Gulf War illness symptom burden with increased activation at peak exercise time in pathways was found, supporting neuronal development along with down regulation of apoptotic signaling. This was accompanied by prolactin-mediated increases in NF-kappa beta activation, a shift in T- and NK-cell populations, and the expression of IL-10 and IL-1 alpha.

Finally, the same group (Smylie et al., 2013) compared cytokines in peripheral blood of 20 male and 10 female Gulf War illness veterans with 12 male and 10 female CFS patients and 21 male and 9 female healthy veterans before, during, and after exercise. Analysis was performed as in the earlier studies. Linear classification models were constructed using stepwise variable selection to identify cytokine coexpression patterns characteristic of each group. Common to the signature of both Gulf War illness and CFS were IL-10 and IL-23 accompanied by NK and Th1 markers in males and Th2 markers in females. Exercise response differed between sexes. Male Gulf War illness veterans presented characteristic signatures at rest, but not at peak exercise effort. The opposite was true for females.

The data analyses that were used in the last four of the above five studies testing the immune network response in veterans groups before, during, and following exercise stress, were nonconventional and hard to interpret. Even the authors discuss the limitations of their approach

saying, "it must be emphasized that our analysis was constrained to a specific set of documented pathways and was by no means comprehensive" (Broderick et al., 2013). In addition to the limited scope of pathways examined, the authors point out that they found the mathematical method of Efroni et al. (2007, 2008), which they used, was conservative and unable to detect the loss of more subtle signaling mechanisms. Also, the number of subjects is small, and the panel of cellular and molecular markers used is relatively narrow and does not represent a complete survey of immune response (Broderick et al., 2011). Therefore, the data from these researchers must be considered preliminary until more information is obtained.

In a small study, Parkitny et al. (2015) tested to see if Gulf War illness was associated either with abnormal concentrations or abnormal fluctuations in pro-inflammatory immune markers in sera. Three hypotheses were tested: First, that serum pro-inflammatory cytokines would be higher in Gulf War illness veterans than in healthy veterans; second, that daily cytokine fluctuations would be greater in Gulf War illness veterans than in healthy veterans; and third, that daily self-reported fatigue in Gulf War illness veterans would covary with the concentrations of pro-inflammatory cytokines. Seven Gulf War illness veterans and eight healthy veterans had daily blood draws and gave daily self-reports on fatigue symptoms for 25 consecutive days. Among the 21 pro-inflammatory cytokines measured, only eotaixn-1 was found to be elevated in the blood of Gulf War illness veterans compared with healthy veterans. Higher self-reported fatigue days were associated with greater concentrations of IL-1b and IL-15. The small size of the study plus the fact that fatigue was self-reported diminished the potential significance of the study.

One study compared cytokines in sera in veterans with Gulf War illness and CFS/ME. Khaiboullina et al. (2015) tested the hypothesis that Gulf War illness resembles CFS/ME and might be a subset of that disease. For the study, 77 cytokines were measured in sera from Gulf War illness veterans (37), patients with CFS/ME (67) and healthy controls (42). The profile of cytokines could be used to delineate Gulf War illness and ME from controls, but the Gulf War illness values resembled control values more than the CFS/ME values. The authors concluded that the two conditions have distinct immune profiles despite their overlapping symptomology.

British physicians have tested the hypothesis that Gulf War illness results from an imbalance in the Th1/Th2 immune system (Skowera et al., 2004). Their subjects consisted of 80 nonsymptomatic Gulf War veterans, 40 symptomatic veterans, 20 symptomatic veterans of peacekeeping duties in Bosnia, and 39 symptomatic veterans in service at the time of the Gulf War but not deployed. The latter two groups were combined (total = 59) to form a control group who had multisymptom illness but had not been in the Gulf War. Peripheral blood CD4+ lymphocytes were stained using appropriate PE-conjugated anti-cytokines and were analyzed by flow cytometry for IL-2, IFN-gamma, IL-4 and IL-10 in the absence of activators. There was considerable overlap in the data but symptomatic GW veterans had significantly higher mean levels of non-stimulated IL-4+ and IL-2+ cells compared to well GW veterans and the control group. After short-term polyclonal stimulation, the cultured cells were found to secrete more IL-10 in the symptomatic Gulf War group than in the nonsymptomatic group. The IL-10 levels were also higher in the control group compared with the nonsymptomatic group. Again, there was considerable overlap in the data. The authors conclude that, even several years after the Gulf War, symptomatic veterans showed evidence of ongoing immune activation which is predominately Th1 and an expansion of IL-10 producing memory cells. The considerable overlap of the data in all three groups indicates that these immune markers could not be used as biomarkers in diagnosis of Gulf War illness. While significant differences were observed, the

biological significance is uncertain. Earlier reviews did not find that immunological responses were abnormal in symptomatic Gulf War veterans (Everson et al., 2002).

While several investigators have attempted to define a cytokine profile unique to Gulf War illness, their studies have not been successful. The committee notes that the findings of Broderick and colleagues are intriguing but preliminary and their significance is uncertain. Nonetheless, the committee observes that there is potential merit in the methodology. It would likely be productive to repeat these transcriptomic studies with several protocol enhancements including expansion of the study cohorts for sufficient power; use of appropriately chosen controls; use of distinct discovery and replication cohorts, each appropriately powered; use of RNAseq methods to analyze the sequences and numbers of all coding and noncoding RNA transcripts in an unbiased manner; and appropriate use of bioinformatics tools to discern specific disease pathways.

Other Studies of Possible Relevance

In a search for persistent enteroviruses, Urnovitz and colleagues (1999) compared levels of circulating RNA in sera from 24 deployed Gulf War veterans and 50 nonmilitary controls. RNA was isolated and amplified with primers from untranslated domains of the enterovirus, longer species of circulating RNAs in sera of Gulf War veterans were detected. Two of these were sequenced and found to map to human chromosome 2q11; they were not enteroviral sequences.

In a series of genes proposed to be relevant to susceptibility to chronic fatigue, Vladutiu and Natalson (2004) studied CFS/idiopathic chronic fatigue in two case-control sets: 49 veterans with CFS and 30 veterans without CFS, and in 61 nonveterans with CFS and 45 nonveterans without CFS. They examined the frequency of gene variants for three proteins: angiotensin converting enzyme, myoadenylate deaminase, and carnitine palmitoyltransferase II. The authors reported that an insertion allele ("I") in intron 16 of the gene encoding angiotensin-converting enzyme (otherwise designated DCP1) is reduced in frequency in Gulf War veterans (0.15) with CFS compared with asymptomatic vets (0.48). Reciprocally, the alternate deletion "D" allele was overrepresented in symptomatic Gulf War veterans (0.85), as was the DD allele (0.78). However, the frequency of the I-allele in symptomatic and asymptomatic nonveterans was the same as the asymptomatic veterans (0.48–0.50). The reduced I-allele was predicted to enhance angiotensin-converting enzyme activity and promote higher angiotensin II levels, a profile that has been associated with adverse outcomes (more coronary artery disease).

Conclusions

Gulf War illness continues to be the signature health concern of veterans who served in the Persian Gulf region in 1990–1991. A variety of studies in U.S. veterans and coalition force veterans who served during and even after the conflict continue to show that veterans who were deployed to the Gulf War experience more symptoms, signs, and ill-defined conditions, and that their symptoms are more severe than their nondeployed counterparts; furthermore, these symptoms have persisted for more than 25 years after the war. In spite of concerted efforts to identify a cause or physiologic mechanism for Gulf War illness, no clear answer has been established. Several new studies report associations between several exposures, particularly to chemicals, and the presence of Gulf War illness, but to date, there are no reliable or validated biomarkers of exposure or symptoms to substantiate the etiology or mechanisms of the illness. Animal toxicology studies of Gulf War illness are discussed in Chapter 5. As noted earlier in this

section, one of the difficulties in studying Gulf War illness is the several case definitions and the variable presentations of this condition.

Studies looking for biomarkers of Gulf War illness or other health conditions face many methodological problems irrespective of the approach or technology used (neuroimaging, genetics, cytokines). In general, such studies are small and often not adequately powered, suffer from multiple comparisons, and focus on nonspecific pathology that may indicate, or be involved in, many different disease pathways, known and unknown. Furthermore, researchers interpret their results as demonstrating positive findings without consideration of the high possibility of type I errors (false positive). Biomarkers, in general, are indicators of current pathology and are not useful or reliable measures of an exposure or an effect occurring many years earlier. They are, however, good for discovering clinically latent or subclinical disease.

Therefore, the Volume 10 committee concludes that there is sufficient evidence of association between deployment to the Gulf War and the constellation of chronic symptoms (including fatigue, musculoskeletal pain, sleep disturbances, cognitive dysfunction, alterations of mood) known as Gulf War illness.

TABLE 4-1 Primary Studies of Gulf War Illness

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Volumes 4 and 8 Primary Studies						
Factor Analyses and Surveys						
Haley et al., 1997b (Vol. 4)	Exploratory factor analysis of 52 symptoms	Active-duty and retired Navy GWVs (n = 249)	Factor-analysis derived syndromes	Impaired cognition Confusion-ataxia Arthromyoneuropathy Phobia-apraxia Fever-adenopathy Weakness-incontinence		Small cohort size, no nondeployed control group Syndromes accounted for 71% of observed variance
Fukuda et al., 1998 (Vol. 4)	Cross-sectional population survey; factor analysis of 35 symptoms to identify symptom categories in combination with clinical reasoning	3,675 members of the Air Force, including National Guard, reserve, and active-duty components (1,155 GWVs and 2,520 NDVs) Factor analysis: n = 3,255	Cases defined as having one or more symptoms from at least two of the three identified symptom categories: Fatigue Mood-cognition Musculoskeletal	GWV vs NDV: Mild-to-moderate cases (449 vs 354) OR = 4.08 (95% CI 3.39–4.93) Severe cases (68 vs 18) OR = 16.18 (95% CI 8.99–29.14)	Rank, sex, age, smoking status	Symptom categories accounted for 39% of common variance
Nisenbaum et al., 2000 (Vol. 8)	Cross-sectional survey	1,002 Air Force GWVs selected from the population described by Fukuda et al. (1998)	Association of self-reported exposures with severe cases (n = 58) and mild-to-moderate (n = 401), as defined by Fukuda et al. (1998)	Belief that biological or chemical weapons were used, severe OR = 3.5 (95% CI 1.7–6.9) and mild/moderate OR = 2.3 (95% CI 1.5–3.3); PB, severe OR = 2.9 (95% CI 1.4–6.1) and mild/moderate OR = 1.6 (95% CI 1.1–2.2); insect repellent, severe OR = 2.4 (95% CI 1.3–4.5) and	Age, sex, smoking status, current rank	All exposures self-reported

Study	Design	Population	Outcomes	Results	Adjustments	Comments
				mild/moderate OR = 1.7 (95% CI 1.2–2.3); injuries requiring medical attention, severe cases only OR = 2.1 (95% CI 1.1–4.3)		
Ismail et al., 1999 (Vol. 4)	Exploratory factor analysis of 52 symptoms (based on survey conducted by Unwin et al., 1999)	3,214 male UK GWVs compared to 1,770 Bosnia veterans and 2,384 nondeployed era veterans	Symptom categories	Mood-cognition Respiratory symptoms Peripheral nervous system symptoms Frequency of symptom reporting higher in GWVs compared to Bosnia and era cohorts, but similar correlations between symptoms for all cohorts		Response rates: GWVs (76%), Bosnia veterans (42%), era veterans (56%) Factor categories accounted for 20% of the common variance
Kang et al., 2002 (Vol. 4)	Exploratory factor analysis of 47 symptoms	10,423 GWVs compared to 8,960 nondeployed era veterans	Symptom clusters; association of symptom clusters with self-reported exposures	Five similar symptom clusters were found in both groups: Fatigue or depression Musculoskeletal/rheumatologic Gastrointestinal Pulmonary Upper respiratory Four symptoms comprised a neurologic cluster that appeared to be unique to GWVs: blurred vision, loss of balance/dizziness, tremors/shaking, and speech difficulty. 277 (2.4%) GWVs reported mild or severe problems with these symptoms vs 43 (0.45%) nondeployed. At		69% response rate in GWVs and 60% in era controls 69% of the GWVs suffering all four symptoms also met criteria for PTSD

Study	Design	Population	Outcomes	Results	Adjustments	Comments
				least 3 out of 4 of these symptoms were observed in 877 (7.7%) GWVs vs 175 (1.8%) nondeployed veterans Exposures associated with four-symptom cases (n = 277) vs nonsymptomatic controls (n = 6730), $p < 0.0001$: Contaminated food (73% vs 21%); nerve gas (42% vs 5%); DU (29% vs 7%); toxic paint (51% vs 16%); bathed in or drank contaminated water (60% vs 19%); sexual assault (3.3% vs 0.4%); sexual harassment (15% vs 3%); botulism vaccine (26% vs 9%)		
Ishoy et al., 1999b (Vol. 4)	Cross-sectional	686 Danish peacekeepers deployed to gulf in 1990–1997 vs 231 age- and sex- matched nondeployed controls	Health examination by physician, including lung function and self-report questionnaire of symptoms	Deployed veterans reported higher prevalence ($p < 0.05$) of 17 out of 22 neuropsychological symptoms, 8 out of 14 gastrointestinal symptoms, and 8 out of 19 skin symptoms 81% of deployed veterans vs 71% of controls had one or more ICD-10 diagnoses at examination ($p = 0.002$)		Participation rate: 83.6% deployed, 57.8% nondeployed
Blanchard et al., 2006 (Vol 8)	Cross-sectional	1,035 GWVs vs 1,116 NDVs	CMI determined by medical examination in 1999–2001	Deployed vs nondeployed: CMI (all cases), 29% vs 16% (OR = 2.16, 95% CI 1.61–2.90) Mild to moderate cases, 25%	Age, sex, race, education, duty type, service branch, rank, income,	Participation rate: 53% deployed, 39% nondeployed

Study	Design	Population	Outcomes	Results	Adjustments	Comments
				vs 15% (OR = 1.92, 95% CI 1.41–2.63) Severe cases, 7% vs 1.6% (OR = 4.65, 95% CI 2.27–9.52)	combat exposure score, Khamisiyah exposure, psychiatric and other diagnoses prior to GW	
Nisenbaum et al., 2004 (Vol. 4)	Dichotomous factor analysis (reanalysis of survey results from Fukuda et al., 1998, and Ismail et al., 1999)	3,454 male UK GWVs compared to 1,979 Bosnia veterans and 2,577 nondeployed era veterans 1,163 deployed U.S. Air Force veterans	Symptom clusters	UK cohort: Identified a cluster of gastrointestinal/urogenital symptoms that loaded to deployed veterans but not to either control group Confirmed factors identified by Ismail et al. (1999) were very similar across all three cohorts U.S. cohort: Gastrointestinal/respiratory Allergies Mood-cognition Musculoskeletal		No control group in U.S. cohort
Hospitalization Studies						
Gray et al., 1996 (Vol 8)	Retrospective cohort, hospitalizations from August 1991 through September 1993	547,076 active-duty U.S. GWVs and 618,335 NDVs	Hospital-discharge diagnoses of circulatory system disease in DoD hospital system (ICD-9 classification)	No increase in any-cause hospitalization among deployed GWVs	Prewar hospitalization, sex, age, race, service branch, marital status, rank, length of service, salary, occupation	Very short follow-up period; no outpatient data; restricted to DoD hospitals, and thus to persons remaining on active duty after

Study	Design	Population	Outcomes	Results	Adjustments	Comments
						the war; no adjustment for potential confounders such as smoking
Knoke et al., 1998 (Vol 8)		552,111 deployed vs 1,479,751 nondeployed U.S. service members in service during Gulf War and remaining there through 1996	Hospitalization records: DoD only, 1991–1996, ICD 799.9 (unexplained illness)	No excess in hospitalizations in this period when effect of CCEP was eliminated	Race, rank, salary, military branch, occupation, prewar hospitalization, sex	Active duty only, no assessment of outpatient treatment, respiratory findings removed after adjustment for VA screening-program attendance
Gray et al., 2000 (Vol 8)	Retrospective cohort, hospitalizations from August 1991 through December 1994	652,979 GWVs, 652,922 randomly selected NDVs: 182,164 DoD hospitalizations; 16,030 VA hospitalizations; 5,185 COSHPD hospitalizations	Hospital-discharge diagnoses in DoD, VA, and COSHPD hospital systems	Similar rates of hospitalization between deployed and nondeployed veterans	Age, sex, race (only for DoD PMR)	Able to assess only illnesses that resulted in hospitalization; possible undetected confounders PMR has lower sensitivity than a comparison of hospitalization rates
Smith et al., 2006 (Vol 8)	Retrospective cohort study (cohort data	Active-duty personnel with a single	Postdeployment hospitalization events (1991–2000)	Veterans of southwest Asia had slightly higher rate of hospitalization compared to	Sex, age, marital status, pay grade,	Lower hazard ratio observed in veterans of

Study	Design	Population	Outcomes	Results	Adjustments	Comments
	from DMDC)	deployment to: Gulf War theater (n = 455,465); southwest Asia peacekeeping mission, 1991–1998 (n = 249,047); Bosnia, 1995–1998 (n = 44,341)		deployed GWVs, while veterans of Bosnia had slightly lower rate of hospitalizations	race/ethnicity, service branch, occupation, and predeployment hospitalization; time-dependent covariate to account for changing hospitalization methods, diagnostic criteria, and procedures	Bosnia may be partially explained by shorter follow-up period Limitations: active-duty personnel only; hospitalizations at DoD facilities only
Volume 10 Primary Studies						
Kelsall, et al., 2009	Cross-sectional comparison of physiological and psychological outcomes in GW deployed vs nondeployed Questionnaire, including CIDI, and medical assessment conducted between 2000–2002	Male Australian veterans randomly sampled: 1,456 GWVs and 1,588 NDVs	Questionnaire included hospitalizations, medications, functional impairment, Alcohol Use Disorders Test, GHQ-12, SF-12, 63-symptom checklist, deployment information. Full medical exam included fitness test, heart rate, blood tests, and evaluation for psychiatric disorders; Gulf War illness defined using CDC definition	26% of GWVs and 16% of NDVs had Gulf War illness (OR = 1.8, 95% CI 1.5–2.2) Gulf War illness in GWVs was associated with stopping the fitness test early (OR = 2.1, 95% CI 1.2–3.8), but not heart rate recovery; increased functional impairment (OR = 4.9, 95% CI 3.7–6.5); occupational impairment (OR = 2.7, 95% CI 1.6–4.5); increased health care utilization (OR = 1.7, 95% CI 1.2–2.4); unexplained chronic fatigue (OR = 13.3, 95% CI 7.7–23.1); elevated neuropathy	Frequency matched on service branch and 3-year age bands	Derivative of Kelsall et al., 2004 Women excluded Response rate: 80.5% in GWVs and 56.8% in NDVs 21% of NDVs had been actively deployed elsewhere

Study	Design	Population	Outcomes	Results	Adjustments	Comments
				score (mean difference = 2.4, 95% CI 1.5–3.8); increased waist circumference (OR = 1.5, 95% CI 1.1–2.0); poorer SF-12 physical health quality of life scores (mean difference = -9.5, 95% CI -10.5–8.5); SF-12 mental health scores (mean difference = -11.1, 95% CI -12.4–9.9); any current psychiatric disorder (OR = 5.0, 95% CI 3.8–6.7) including affective disorders, major depression, anxiety, PTSD, somatoform disorders, and alcohol use/dependence (all ORs > 2 and $p < 0.05$); inflammation (OR = 1.6, 95% CI 1.1–2.3); and elevated random glucose (OR = 6.9, 95% CI 1.5–41.9) compared to healthy controls. Gulf War illness in GWVs not associated with spirometry performance, lung function, blood pressure, anemia, renal impairment, obstructive or inflammatory liver disease, or prior exposure to EBV or CMV compared to healthy controls		This study shows importance of psychiatric disorders for classification of those who meet definitions of Gulf War illness and lack of routine physiologic signs
Sim et al., 2015 (Australian Veterans	Cohort study Longitudinal health survey conducted in	All Australian Gulf War veterans eligible Health survey:	Self-reported symptoms based on 63-item checklist Gulf War illness	GWVs had a sig higher prevalence of 47 symptoms than NDVs Both groups reported sig more		Participation rate: 54% in GWVs and 47% in NDVs First

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Study)	2011; mortality and cancer registry studies	715 GWVs and 675 NDVs; mortality and cancer registry study: 1,871 GWVs and 2,922 NDVs	diagnosed using CDC definition	symptoms at follow-up than baseline Risk of Gulf War illness increased in both groups from baseline to follow-up: GWVs RR = 1.27 (95% CI 1.11–1.44) and NDVs RR = 1.19 (95% CI 0.97–1.47) Gulf War illness at follow-up in GWVs vs NDVs RR = 1.6 (95% CI 1.31–1.95)		survey conducted in 2003 Derivative of Kelsall et al. (2009)

NOTE: CCEP = Comprehensive Clinical Evaluation Program; CDC = Centers for Disease Control and Prevention; CI = confidence interval; CIDI = Composite International Diagnostic Interview; CMI = chronic multisymptom illness; CMV = cytomegalovirus; COSHPD = California Office of Statewide Health Planning and Development; DMDC = Defense Manpower Data Center; DoD = Department of Defense; DU = depleted uranium; EBV = Epstein-Barr virus; GHQ = General Health Questionnaire; GW = Gulf War; GWV = Gulf War veteran; ICD = International Classification of Diseases; NDV = nondeployed veteran OR = odds ratio; PB = pyridostigmine bromide; PMR = proportional morbidity ratio; PTSD = posttraumatic stress disorder; RR = risk ratio; SF-12 = 12-item short form health survey; U.S. = United States; UK = United Kingdom; VA = Department of Veterans Affairs.

CANCER

Cancer can develop at any age, but the median age for any type of cancer diagnosis is 65 years (National Cancer Institute, 2015). The National Cancer Institute's Surveillance, Epidemiology, and End Results Program estimates incidence, prevalence, and deaths from all cancers and site-specific cancers using age-adjusted rates and actual cases and deaths from 2008–2012. The overall incidence rate for all cancer sites in 2015 was estimated to be 454.8 per 100,000 people per year, or a total of 1,658,370 new cases that year (National Cancer Institute, 2015). Based on 2010–2012 data, approximately 40% of U.S. men and women will be diagnosed with cancer (that is, a malignant neoplasm) at some point during their lifetime (National Cancer Institute, 2015). As of January 1, 2014, approximately 14.5 million people in the United States had a history of a cancer diagnosis (American Cancer Society, 2015). Cancer usually has a long latency period (≥ 20 years) (Cogliano et al., 2004), and, therefore, many Gulf War veterans are still young for cancer diagnoses (the mean age of military personnel during the Gulf War in 1991 was 28 years). However, some forms of cancers—such as testicular cancer, skin cancer, leukemia, lymphoma, and brain cancer—may also develop in younger people or may have shorter latency periods.

Relatively few studies of Gulf War veterans have focused on cancer incidence or prevalence; rather, the majority of studies on the association between overall or cause-specific cancers and Gulf War deployment are mortality studies, which are discussed in the section on causes of mortality. All primary studies of cancer morbidity are summarized in Table 4-3 at the end of this section.

Summary of Volumes 4 and 8

The Volume 4 committee reviewed four cancer studies and found no consistent evidence of a higher overall incidence of cancer in Gulf War veterans than in nondeployed veterans. However, the committee also noted that many veterans were young for a cancer diagnosis and, for most cancers, the follow-up period after the Gulf War was probably too short to expect the onset of most cancers. The incidence of cancer in general, and testicular cancer in particular, have been assessed in cohort studies. Two studies focused on the risk of developing testicular cancer, but results were inconsistent: one study concluded that there was no evidence of an excess risk (Knoke et al., 1998), and the other, a small registry-based study, suggested there may be an increased risk but no definitive conclusions could be made because few cases were identified (Levine et al., 2005). One study examined cancer of all sites. The first study examined incident cases of all cancer in UK Gulf War deployed and nondeployed veterans in the 10 years following the conflict, but after adjusting for sex, age group, service branch, and rank found no evidence of an association between deployment to the gulf and development of cancer (Macfarlane et al., 2003). The Volume 4 committee concluded that additional follow-up time was needed to assess the association between deployment and development of site-specific cancers.

The Volume 8 committee reviewed three primary studies and ten secondary studies. No consistent evidence of a higher overall incidence of cancer was found in veterans who were deployed to the Gulf War versus nondeployed veterans. Two primary studies found no statistically significant increase in hospitalizations from neoplasms in Gulf War veterans

compared with their nondeployed counterparts. A third primary study found no association between deployment and any cancer, including brain, testicular, and digestive tract, among Canadian Gulf War veterans. The Volume 8 committee concluded that there was insufficient/inadequate evidence of an association between Gulf War exposures and brain cancer. Mixed results for testicular cancer were reported by the Volume 4 committee, and the Volume 8 committee did not identify any new studies of this cancer site. The Voluem 8 committee agreed with the Volume 4 committee in that many veterans were still too young for cancer diagnoses, and the follow-up period was too short for most cancers. Therefore, the Volume 8 committee found that further follow-up was necessary to be able to make a conclusion about whether there is an association between deployment during the Gulf War and any cancer outcomes. *The Volume 8 committee concluded that there was insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and any cancer. The committee also recommended that due to the long latency period for cancer, there needed to be continued follow-up of Gulf War veterans and an appropriate comparison group to adequately determine any association.*

New Literature

The Volume 10 committee identified three new studies of cancer in Gulf War veterans; two were deemed primary studies, one was considered a secondary study.

Primary Studies

The first primary study was the Australian Gulf War Veterans' Follow-Up Health Study (Sim et al., 2015) that examined cancer incidence rates through 2008 in the entire cohort of 1,871 Australian Gulf War veterans and a comparison group of 2,922 veterans frequency matched based on age, sex, rank category, and service branch. Incident cancers were identified and linked to the cohort using the Australian Cancer Database, which collects data on all primary, malignant cancers diagnosed in Australia since 1982, but does not include basal cell or squamous cell carcinomas of the skin, cancer recurrences, or metastases. Data includes date of cancer diagnosis, site, histology, Australian state in which the cancer was diagnosed, date of death (if applicable), and the ICD-10 codes for the type of cancer. Cancer diagnoses were presented as all malignant neoplasms; lip cancer; colorectal; other digestive organs; lung, trachea, and bronchus; melanoma; prostate; testis; kidney; brain and other central nervous system cancers; thyroid; all lymphomas; and leukemia. Hazard ratios (HRs) were used to make comparisons between the two veteran groups and standardized incidence ratios were used to make comparisons between each veteran group and the Australian population.

Because women veterans composed only 2% of the Australian deployed cohort, and no deployed women developed cancer in the 18-year follow-up, women were excluded from the cancer incidence analyses. A total of 115 cancers were observed among the male veterans, affecting about 2.5% of the total male cohort. No significant differences between the deployed and the comparison group were found for all malignant cancers (adjusted HR = 1.20, 95% CI 0.83–1.73) or any type of cancer. For site-specific cancers, there were fewer than five cases observed for deployed or comparison groups for several sites including colorectal; brain and other parts of the central nervous system; testis; lung, trachea, and bronchus; kidney; thyroid; lip; and leukemia. No significant differences were observed between deployed veterans and the Australian male population for site-specific cancers; however, few incident cancers were available for analysis and the power of this study to identify rare cancers was low. There was a

statistically significant risk for thyroid cancer calculated on the basis of standardized incidence ratios (SIR = 2.89, 95% CI 1.20–6.93), although this estimate was based on only five cases of thyroid cancer observed in the comparison veterans, which limits the conclusions that can be drawn. The number of brain cancer cases, while not statistically significant and based on less than five cases, was higher than expected among Gulf War veterans compared to the general Australian population (SIR = 2.38, 95% CI 0.89–6.35). The authors concluded that "In the 18 year period since the Gulf War, there have been no statistically significant differences in cancer incidence of any type between the male Gulf War veterans, the male comparison group members, and the same-aged Australian male population."

The committee notes that while the Australian study adjusted for some factors—such as age, service branch, and rank—the study did not adjust for other important potential confounders such as smoking, body mass index, and alcohol use.

The second primary study examined proportional cancer incidence among all 621,902 U.S. veterans deployed to the Gulf War and 746,248 era veterans (Young et al., 2010). Era veterans were a stratified random sample of veterans from all military personnel who served during the conflict but were not deployed to the Persian Gulf region. Veterans diagnosed with cancer between 1991 and 2006 were identified using data from the Defense Manpower Data Center (DMDC), which was linked to central cancer registries in 28 states and the VA Central Cancer Registry. The 28 state registries captured 84% of the U.S. population, based on the 2000 Census; cancer cases were grouped into 30 categories. Logistic regression models that controlled for age, race, and sex were used to determine whether the proportion of veterans with a diagnosed cancer differed between deployed and era veterans. Crude and adjusted proportional incidence ratios (PIRs) were calculated to determine differences by specific cancer type; adjustment was made for sex, diagnosis age, diagnosis age squared, diagnosis year, race, branch of service, unit type, and registry group. For cancer types with statistically significant adjusted PIRs, SIRs were calculated. The SIRs compared the Gulf War veterans and era veterans with the general population, adjusted for sex, race, and age.

A total of 21,075 incident cancer diagnoses were identified—8,211 among the deployed veterans and 12,864 among the era veterans—of these, 2,796 were identified from the VA Central Cancer Registry. No statistically significant association was found between deployment status and the proportion of veterans diagnosed with cancer (OR = 0.99, 95% CI 0.96–1.02). No difference in proportional incidence between deployed and era veterans was found for brain cancer (PIR = 0.86, 95% CI 0.73–1.01), melanoma (PIR = 0.98, 95% CI 0.89–1.09), other skin cancers (PIR = 0.82, 95% CI 0.53–1.28), digestive system cancers (PIR = 1.07, 95% CI 0.97–1.18), or leukemia (PIR = 0.93, 95% CI 0.78–1.12). Lung cancer was the only site-specific cancer found to have a significantly higher proportion among deployed veterans compared with era veterans (PIR = 1.15, 95% CI 1.03–1.29). It remained significant when further analysis compared proportional incidence of lung cancer in Army and Marine veterans with era veterans (PIR = 1.21, 95% CI 1.07–1.38). Two types of cancers had statistically significantly decreased proportional incidence ratios in deployed veterans compared with nondeployed veterans: testicular cancer (PIR = 0.85, 95% CI 0.75–0.98) and Kaposi sarcoma (PIR = 0.54, 95% CI 0.37–0.79). SIRs comparing deployed and era veterans with the general U.S. population were calculated for lung cancer, testicular cancer, and Kaposi sarcoma. Neither deployed nor era veterans showed significantly increased risks of lung or testicular cancer compared to the general population. Both of these veteran groups had significantly decreased risks of Kaposi sarcoma

when compared with the general population (SIR deployed = 0.08, 95% CI 0.05–0.12; SIR era = 0.18, 95% CI 0.13–0.24).

The committee notes that as with the Australian cohort study, Young and colleagues were able to adjust for some demographic, diagnostic, or military factors, but no data on smoking status were available, and therefore, this factor was not included in the adjusted effect models. The length of follow-up was, at most, 15 years, which may not be enough time for certain cancers such as lung cancer to develop if there were a Gulf War etiologic factor. Additionally, the numbers of incident cancer diagnoses are likely to be underestimated because 22 states were not represented, which may alter the PIR as it is affected by the relative frequencies of other cancer types. Also, of the 28 state registries that were included, not all covered the full time period. Major strengths of the study are that it used the entire population of deployed Gulf War veterans and a large and representative sample of era veterans, and that it used cancer registry data—as opposed to mortality, hospitalization, or self-reported diagnoses—to assess cancer incidence outcomes. For more frequently occurring cancers such as lung, prostate, and melanoma, the sample sizes were large enough to provide adequate statistical power to detect relatively small differences between veteran groups and between each veteran cohort and the general U.S. population.

Secondary Studies

The wave 3 survey of the cross-sectional National Health Study of Persian Gulf War Era Veterans was conducted in 2012–2013 and asked 8,104 deployed and 6,148 Gulf War era veterans four questions pertaining to cancer: whether a doctor ever told the veteran that they had skin cancer (other than melanoma), melanoma, brain cancer, or any other cancer, with space to write in what that cancer was (Dursa et al., 2016). If the veteran responded yes, they were asked whether the condition had been present in the past 4 weeks.

Weighted prevalence and adjusted odds ratios (models were adjusted for age, race, sex, BMI, smoking status, service branch, and unit component) were presented for the four self-reported cancer questions among deployed and era veterans. No statistically significant differences between deployed and era veterans were observed for weighted reports (cases) of skin cancer (4.4% [488 cases] vs 5.4% [418 cases]; OR = 1.06, 95% CI 0.88–1.29), melanoma (2.5% [230 cases] vs 2.7% [183 cases]; OR = 1.15, 95% CI 0.87–1.52), or other cancers (5.2% [505 cases] vs 5.6% [399 cases]; OR = 1.12, 95% CI 0.91–1.37). The number of brain cancer cases was small: 30 among the deployed and 19 among the era veterans (0.3% each; OR = 1.02, 95% CI 0.47–2.21) (Dursa et al., 2016). Bossarte (2014) presented additional results to the committee on weighted cases of self-reported brain cancer among deployed and era veterans by service branch, but no significance testing was performed.

Other Related Studies

VA provided a health care use report for Gulf War deployed and era veterans who sought care in VA facilities from October 2001 to December 2013. The report presented the prevalence of diagnoses of diseases by ICD-9 code categories, including the top 10 malignant cancers (ICD-9-CM 140–209) (see Table 4-4); no statistical testing was performed. 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. A total of 286,995 Gulf War deployed and 296,635 era veterans received treatment at VA over the approximately 11-year period (VA, 2014a,b). These VA health care users represent 46% of all

deployed Gulf War veterans and 36% of all nondeployed era veterans. In addition to the malignant neoplasms in Table 4-4, a total of 43,337 benign neoplasms were diagnosed among deployed veterans, and 43,757 benign neoplasms were diagnosed among nondeployed veterans.

TABLE 4-4 Ten Most Frequent Malignant Neoplasm Diagnoses for Deployed and Nondeployed Gulf War Veterans Seeking Health Care in VA Between 2002 and 2013

Diagnosis	Deployed N = 14,572 (%)	Nondeployed N = 17,105 (%)
Other malignant neoplasm of skin	23.6	23.8
Malignant neoplasm of prostate	22.1	24.4
Malignant melanoma of colon	6.2	5.7
Malignant neoplasm of trachea, bronchus, and lung	6.0	6.3
Malignant neoplasm of skin	5.3	5.1
Other malignant neoplasms of lymphoid, histiocytic tissue	5.2	5.0
Secondary malignant neoplasm of other specified sites	4.4	4.1
Malignant neoplasm of kidney and other unspecified urinary organs	4.1	3.8
Malignant neoplasm without specification of site	4.0	3.8
Malignant neoplasm of female breast	3.8	5.9

SOURCE: VA (2014a,b).

Conclusions

Given the lack of new evidence on the effect of deployment to the Gulf War and incidence of overall or site-specific cancers from two primary studies, the committee concurs with the conclusions of the Volume 8 committee that there is insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and the incidence or prevalence of any cancer. (Cancer mortality is discussed in the section on causes of morality.) However, the committee also concurs with the Volume 8 committee's recommendation that because many cancers have long latency periods, follow-up of deployed Gulf War veterans and an appropriate comparison group of era veterans should be continued to adequately determine whether there is an association.

Brain and lung cancer have been of particular concern to Gulf War veterans (see statement of task in Chapter 1). Both of the new primary studies reported on these cancers, but neither provided evidence of an increased risk for these cancers among Gulf War veterans. Young et al. (2010) found a higher proportion of lung cancer in Gulf War veterans compared with era veterans, but there was no difference when compared to the general population. Moreover, Young et al. (2010) made no adjustment for smoking status in their analyses. The CDC (2014) estimates that cigarette smoking is linked to 90% of lung cancers. No statistically significant differences for brain cancer were identified in either of the primary studies. Volumes 4 and 8 described studies (Bullman et al., 2005; Barth et al., 2009) that reported an increased risk of brain cancer mortality potentially associated with demolition of chemical munitions at Khamisiyah, however these authors based exposure on a plume model for which there is

considerable uncertainty (GAO, 2004). The committee thus concurs with the Volume 4 and 8 committees that there is insufficient/inadequate evidence of an association between demolitions at Khamisiyah and an increased risk of brain cancer. The committee finds that follow-up of cancer prevalence and incidence has only been conducted through 2006 (15 years since the Gulf War), which may not account for latency periods of 25 years or longer. Because cancer incidence in the last 10 years has not been reported, additional follow-up is needed.

Therefore, the Volume 10 committee concludes that there is insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and any form of cancer, including lung cancer and brain cancer.

TABLE 4-3 Cancer

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Volumes 4 and 8 Primary Studies						
Testicular Cancer						
Knoke et al., 1998 (Vol. 4)	Cohort study (follow-up of Gray et al., 1996)	517,223 active-duty male U.S. GWV and 1,291,323 NDVs	First diagnosis of testicular cancer at U.S. military hospitals worldwide (7/31/1991–3/31/1996)	GWVs (134 cases) vs NDVs (371 cases) RR = 1.05 (95% CI 0.86–1.29)	Race or ethnicity, age, occupation	Short follow-up time, but right age range; no specific exposures evaluated; military hospitals only
Levine et al., 2005 (Vol. 4)	Population based survey—pilot study	All U.S. GWV (incl. reserves) and random sample of NDVs; 621,902 GWVs and 746,248 NDVs	Testicular cancers diagnosed 1991–1999 and registered by DC or NJ cancer registries	GWVs (cases = 17) vs NDVs (cases = 11) (358 males with cancer) PIR = 2.33 (95% CI 0.95–5.70)	Age, state of residence, deployment status, race	
Gray et al., 1996 (Vol. 4)	Hospitalization from August 1991 through September 1993	547,076 active-duty GWVs, 618,335 NDVs	Hospital-discharge diagnoses of testicular cancer (ICD-9-CM Code 186)	GWVs vs NCV Last 5 months of 1991: 29 cases vs 14 cases, SRR = 2.12 (95% CI 1.11–4.02) 1992: SRR = 1.39 (95% CI 0.91–2.11) 1993: SRR = 0.89 (95% CI 0.54–1.44)	Prewar hospitalization, sex, age, race, service branch, marital status, rank, length of service, salary, occupation	Limitations: restricted to persons remaining on active duty after the war, and thus does not include veterans who may have left the service due to poor health; no adjustment for other potential confounders
All Cancers						
Macfarlane et al., 2003 (Vol. 4)	Cohort (follow-up of Macfarlane et al., 2000)	51,721 UK GWVs, 50,755 NDVs; random samples Subgroup of 28,518 GWVs and 20,829 NDVs veterans with	Cancers identified from National Health Service Central Register; first diagnosis 4/1/1991–7/31/2002	GWVs (cases = 270) vs NDVs (cases = 269) Main study: RR = 0.99 (95% CI 0.83–1.17) Subgroup: RR = 1.12 (95% CI 0.86–1.45)	Main analysis: sex, age group, service branch, rank Subgroup: smoking, alcohol use	Follow-up period shorter than expected latency for most cancers; low age; grouped all cancer sites due to low numbers of occurrences

Study	Design	Population	Outcomes	Results	Adjustments	Comments
		records of smoking and alcohol use				
Gray et al., 2000 (Vol. 8)	Retrospective cohort, hospitalization from August 1991 through December 1994	652,979 GWVs, 652,922 randomly selected NDVs 182,164 DoD hospitalizations; 16,030 VA hospitalizations; 5,185 COSHPD hospitalizations	Hospital-discharge diagnoses of neoplasms in DoD, VA, and COSHPD hospital systems	DoD PMR = 0.98 (95% CI 0.94–1.01) VA PMR = 0.88 (95% CI 0.78–0.98) COSHPD = PMR 0.86 (95% CI 0.61–1.1)	Age, sex, race	Able to assess only illnesses that resulted in hospitalization; possible undetected confounders
Statistics Canada, 2005 (Vol. 8)	Retrospective cohort study (based on Goss Gilroy, Inc., 1998) Approximately 2200 deployed Canadians in region during combat	5,117 Canadian GWVs; 6,093 NDVs, frequency matched for age, sex, and military duty status	Cancer incidences determined from CCD through 1999	Incidence of any cancer (HR = 0.86, 95% CI 0.54–1.39) ; cancer of the digestive system (HR = 2.00, 95% CI 0.62–6.12) ; testicular cancer (HR = 0.76, 95% CI 0.18–3.24) ; cancer of the lymph nodes (HR = 0.65, 95% CI 0.16–2.62)	Age, rank	Small sample size with low statistical power; young age of cohort; short follow-up period; no information on confounding factors
Smith et al., 2006 (Vol. 8)	Hospitalization cohort study (cohort data from DMDC)	Active-duty personnel with a single deployment to: Gulf War theater (n = 455,465); Southwest Asia peacekeeping mission, 1991–1998 (n = 249,047); Bosnia, 1995–1998 (n =	Postdeployment hospitalization events (1991–2000) for an ICD-9-CM diagnosis of malignant neoplasm, and for testicular cancer specifically	Veterans of Bosnia and of SW Asia compared to GWV Any neoplasm: Bosnia HR = 0.61 (95% CI 0.50–0.76) SW Asia HR = 1.03 (95% CI 0.93–1.15) Testicular cancer: Bosnia HR = 0.80 (95% CI 0.27–2.39) SW Asia HR = 0.64 (95% CI 0.32–1.28)	Sex, age, marital status, pay grade, race/ethnicity, service branch, occupation, and predeployment hospitalization; time-dependent covariate to account for	Active-duty personnel only; hospitalizations at DoD facilities only

Study	Design	Population	Outcomes	Results	Adjustments	Comments
		44,341)			changing hospitalization methods, diagnostic criteria, and procedures	
Volume 10 Primary Studies						
Sim et al., 2015	Cohort study Longitudinal health survey conducted in 2011; mortality and cancer registry studies	All Australian Gulf War veterans eligible to deploy Mortality and cancer registry study: 1,871 GWVs and 2,922 NDVs	Self-reported doctor-diagnosed disorders Cancer incidence and mortality (SIR, SMR, and HR) based on Australian Cancer database	GWVs vs NDVs Other skin cancer: RR = 0.98 (95% CI 0.8–1.2); Malignant melanoma: RR = 1.25 (95% CI 0.62–2.52) All malignant cancer: HR = 1.2 (95% CI 0.83–1.73) Brain cancer: SIR = 2.38 (95% CI 0.89–6.35) GWVs vs Australian general male population Cancer incidence and mortality (SIR and SMR) were not elevated for any cancer type, nor were there more cancers in GWVs compared with NDVs		No female cancer deaths identified, 4 cases of breast cancer, reported results limited to men No smoking adjustment Follow-up to Sim et al., 2003
Young et al., 2010	Cohort study Cancer cases diagnosed between 1991 and 2006 from SEER and the VA Central Cancer Registry	8,211 cancer cases among 621,902 GWVs and 12,864 cancer cases among 746,848 NDVs	Incident cancer cases and proportional incidence ratios	Only lung cancer had an increased proportional incidence ratio in GWVs vs NDVs (620 vs 966 cases; PIR = 1.15, 95% CI 1.03–1.29) Decreased PIRs were found for testicular cancer (496 vs 590 cases, PIR = 0.85, 95% CI 0.75–0.98) and Kaposi sarcoma (46 vs 85 cases, PIR = 0.54, 95% CI 0.37–0.79) Compared to the general population, SIRs for lung cancer	Analyses controlled for age, race, and sex SIRs adjusted for age and included white males only	Record linkage only represents VA data and SEER data from 28 states; other states are unknown, thus these results may represent an underestimate of the 15-year incidence No smoking data available (GWVs reported to smoke more than NDVs) Follow-up to Levine et al.,

Study	Design	Population	Outcomes	Results	Adjustments	Comments
				were not elevated in either GWVs or NDVs; SIR for testicular cancer in NDVs was 1.1 (95% CI 1.0–1.2); and SIRs for Kaposi sarcoma showed sig decreased risk in both GWVs and NDVs All other comparisons and sites were not significant		2005 (reported in Volume 8) PIR of a cancer site is affected by the relative frequencies of other cancer types

NOTE: BIRLS = Beneficiary Identification Records Locator System; CCD = Canadian Cancer Database; CI = confidence interval; COSHPD = California Office of Statewide Health Planning and Development; DC = District of Columbia; DMDC = Defense Manpower Data Center; DoD = Department of Defense; GW = Gulf War; GWV = Gulf War veteran; HR = hazard ratio; ICD = International Classification of Diseases; NDI = National Death Index; NDV = nondeployed veteran; NJ = New Jersey; PIR = proportional incidence ratio; PMR = proportional morbidity ratio; RR = risk ratio; SEER = Surveillance Epidemiology and End Results; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRR = standardized rate ratio; U.S. = United States; UK = United Kingdom; VA = Department of Veterans Affairs.

BLOOD AND CIRCULATORY SYSTEM CONDITIONS

Cardiovascular disease is a broad term for any disorder of the heart or the blood vessels, such as atherosclerosis and hypertension. Cardiovascular disease, which includes coronary heart disease and stroke, is the leading cause of death for both women and men in the United States.

Conditions of the blood and blood-forming organs include conditions affecting blood cells (erythrocytes, leukocytes, platelets) as well as the organs where these cells are produced (bone marrow, lymph nodes, spleen). The etiology of these disorders is varied, and can include genetic conditions, exposure to toxins and medications, infections, and nutritional deficiencies. All primary studies of conditions of the blood and circulatory system are summarized in Table 4-5 at the end of this section.

Summary of Volumes 4 and 8

As reported in Volume 4, two primary studies (Eisen et al., 2005; Smith et al., 2003) found no statistically significant differences in the prevalence of cardiovascular disease between deployed and nondeployed Gulf War veterans. In the secondary studies, which included hospitalization studies, deployed veterans were generally more likely to self-report hypertension and palpitations, but those reports were not confirmed by medical evaluations. Thus, the Volume 4 committee concluded that there was no difference in the prevalence of cardiovascular disease between deployed and nondeployed Gulf War veterans.

Primary studies of hospitalizations for cardiovascular conditions reviewed in Volume 8 (Gray et al., 1996, 2000; Smith et al., 2002, 2006) did not find an increased risk in deployed versus nondeployed veterans during the first 10–15 years after the Gulf War. The few studies measuring blood pressure in deployed and nondeployed veterans also found no differences between the two groups (Ishoy et al., 1999b; Kelsall et al., 2004a). The only study that found an increase in cardiovascular disease assessed cardiac dysrhythmia in deployed veterans who were possibly exposed to the Khamisiyah plume compared with those who were not exposed (Smith et al., 2003). No studies confirmed this association in other populations, nor was there an increase in hospitalizations for cardiac disease in veterans exposed to smoke from oil-well fires (Smith et al., 2002).

Seven secondary studies provided self-reported prevalence of different cardiovascular conditions, including high blood pressure, palpitations, stroke, heart attacks, and unspecified heart problems by deployment status (Stretch et al., 1995; Proctor et al., 1998; Kelsall et al., 2004a; Steele, 2000; Kang et al., 2000, 2009; Page et al., 2005a; Goss Gilroy Inc., 1998; Simmons et al., 2004). In these studies, deployed veterans were generally more likely to self-report hypertension, palpitations, and other cardiovascular disease, but those reports were not confirmed by clinical evaluations.

Conditions of the blood were not considered as distinct health conditions in Volume 4; however, the Volume 8 committee identified five primary studies that examined hospitalization rates for blood disorders in deployed and nondeployed veterans (Gray et al., 1996, 2000; Smith et al., 2002, 2003, 2006). Overall, these studies did not show that the prevalence of blood disorders was different in deployed Gulf War veterans versus nondeployed veterans. However, these studies precluded any firm conclusions being drawn because hospitalizations were mostly restricted to DoD hospitals, the studies lacked information on outpatient visits where patients

with mild disorders are most likely to be seen, most studies lacked information on potential confounders, and none of them differentiated between specific hematologic disorders. Two other primary studies measured hematologic parameters in Danish and Australian Gulf War veterans compared with nondeployed veterans, but neither showed any major difference by deployment status (Ishoy et al., 1999b; Sim et al., 2003). The two studies were limited by different participation rates for deployed and nondeployed veterans—suggesting a bias—and lacked adjustment for confounding variables. Additionally, studies of blood disorders are limited by the nature of the disease; some blood disorders typically have a long latency, and hospitalization and mortality studies are poor approaches to detect their prevalence and incidence. *The Volume 8 committee concluded that there was inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and cardiovascular disorders or disorders of the blood and blood-forming organs.*

New Literature

The Volume 10 committee did not identify any new primary studies on the risk of Gulf War veterans having conditions of the cardiovascular system.

Secondary Studies

Three secondary studies were identified. One study assessed cardiovascular outcomes in deployed and nondeployed Australian veterans and two studies assessed them in U.S. Gulf War veterans.

The Australian Gulf War Veterans' Follow-Up Health Study, conducted between 2011 and 2013, assessed the entire Australian Gulf War cohort 10 years after the 2000–2002 baseline study and 20 years after the war (Sim et al., 2015). This study was a follow-up to the Kelsall et al. (2004b) baseline study discussed in Volumes 4 and 8. Results were adjusted for age, rank category, and service branch, but not for smoking. Of the 1,456 eligible deployed veterans, 715 participated in the study and 675 of the 1,449 nondeployed veterans provided the comparison group. Health outcomes were based on self-reports and on self-reports of doctor-diagnosed conditions. Deployed veterans were slightly but not significantly more likely to report high blood pressure (RR = 1.14, 95% CI 0.95–1.37) and angina (RR = 1.26, 95% CI 0.51–3.10) but less likely to report having had a heart attack or myocardial infarction (RR = 0.91, 95% CI 0.51–1.63). High cholesterol was the most prevalent medical condition reported by both groups; 35.4% of deployed veterans and 33.2% of nondeployed veterans reported having this diagnosis, but no statistically significant difference between groups was found (RR = 1.13, 95% CI 0.98–1.32).

In 2005, Li et al. (2011a) reported on findings from the 10-year follow-up survey of U.S. Gulf War deployed (n = 5,469) and nondeployed veterans (n = 3,353) who had also participated in the 1995 National Health Survey of Gulf War Veterans and Their Families. Compared with nondeployed veterans, deployed veterans were less likely to report having hypertension (RR = 0.85, 95% CI 0.76–0.96), although they were more likely to report a new incidence of it (RR = 1.15, 95% CI 1.02–1.29). Deployed veterans were also more likely to report the persistence of coronary heart disease, but not significantly so (RR = 1.14, 95% CI 0.70–1.86), and they had a statistically significantly increased risk of new onset of coronary heart disease (RR = 1.61, 95% CI 1.17–2.23). The risk ratios were adjusted for age in 2005, gender, race, rank, service branch, service type, BMI, and current cigarette smoking.

The wave 3 survey of the cross-sectional National Health Study of Persian Gulf War Era Veterans was conducted in 2012–2013 and asked 8,104 deployed and 6,148 Gulf War era veterans to indicate whether a doctor had ever told them they had a medical condition and then whether the condition had been present in the previous 4 weeks. There was a significant difference between the deployed and era veterans in self-reports of tachycardia (8.1% vs 5.9%; OR = 1.47, 95% CI 1.20–1.79), coronary heart disease (5.6% vs 5.3%; OR = 1.32, 95% CI 1.09–1.59), and hypertension (43.0% vs 40.0%; OR = 1.22, 95% CI 1.10–1.35); the prevalence of stroke was not significantly different between the two groups (2.2% vs 2.4%; OR = 0.99, 95% CI 0.75–1.32) (Dursa et al., 2016). The ORs were adjusted for age, race, sex, BMI, smoking status, service branch, and unit component.

Other Related Studies

VA provided a health care utilization report for Gulf War deployed and era veterans who sought care in VA facilities from October 2001 to December 2013. The report presented the prevalence of diagnoses of diseases by ICD-9 code categories, including diseases of the blood and blood-forming organs and diseases of the circulatory system (ICD-9-CM 280-289) (Table 4-6). 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. A total of 286,995 Gulf War deployed and 296,635 era veterans received treatment at VA over the approximately 11-year period (VA, 2014a,b). These VA health care users represent 46% of all deployed Gulf War veterans and 36% of all nondeployed era veterans.

Other studies have assessed the effect of a co-occurring health condition on the prevalence of coronary heart disease, hypertension, and tachycardia. Based on responses to the Patient Health Questionnaire component of the second wave of the VA National Health Survey of Gulf War Era Veterans, Coughlin and colleagues (2011a) found that among 6,111 Gulf War deployed and 3,859 era veterans, deployed veterans, regardless of their weight status (underweight, normal weight, overweight, or obese), self-reported more coronary heart disease and hypertension than nondeployed veterans. No information on diet or physical activity was provided. Further assessment of these veterans found that self-reported hypertension was more prevalent in both deployed and nondeployed veterans with problem drinking (33.4% vs 33.5%) than in deployed and nondeployed veterans without problem drinking (29.4% vs 27.5%). Similar results were also seen for self-reported tachycardia, where deployed veterans with and without problem drinking had an increased prevalence compared with nondeployed veterans (16.6% vs 11.4% and 13.7% vs 9.9%, respectively) (Coughlin et al., 2011b). Heavy drinking was defined as ≥ 15 drinks/week.

Abouzeid et al. (2012) assessed the co-occurrence of PTSD and hypertension in Australian veterans who had deployed to the Gulf War. They found that in 2000–2002, among the 1,381 veterans for whom medical information and results of the CIDI for diagnosing PTSD were available, 100 veterans were considered to have probable hypertension. The ORs for hypertension were 2.90 (95% CI 1.19–7.09) for veterans with PTSD in the past 12 months (n = 71) and 2.27 (95% CI 1.01–5.10) for lifetime prevalence (n = 91), compared with veterans without PTSD (n = 1,290 and 1,310, respectively). The ORs were adjusted for age, occupation, education, marital status, service branch, military service experience, questionnaire score, military rank, BMI, waist circumference, pack-years of smoking, AUDIT case status, and the presence of affective disorders or anxiety disorders other than PTSD.

TABLE 4-6 Ten Most Frequent Diagnoses of Diseases of the Circulatory and Blood and Blood-Forming Organ Systems for Deployed and Nondeployed Gulf War Veterans Seeking Health Care in VA Between 2002 and 2013

Diagnosis	Deployed (%)	Nondeployed (%)
Diseases of the Circulatory System (ICD-9 390-459)	N = 138,489	N = 131,363
Essential hypertension	81.2	81.0
Hemorrhoids	16.8	17.0
Cardiac dysrhythmias	12.7	13.4
Other forms of chronic ischemic heart disease	11.6	13.5
Ill-defined descriptions, complications of heart disease	4.0	4.3
Other peripheral vascular disease	3.2	4.0
Heart failure	2.9	3.4
Other disorders of circulatory system	2.8	3.2
Orthostatic hypotension	2.8	Not reported
Other diseases of the endocardium	2.7	3.2
Diseases of Blood and Blood-Forming Organs (ICD-9 280-289)	N = 28,305	N = 28,307
Other, unspecified anemias	55.7	57.7
Diseases of white blood cells	21.0	19.5
Iron deficiency anemias	18.8	21.4
Other diseases of blood, blood-forming organs	10.8	9.8
Purpura, other hemorrhagic conditions	9.8	9.4
Other deficiency anemias	6.9	6.9
Hereditary hemolytic anemias	6.2	6.0
Coagulation defects	4.0	4.3
Aplastic anemia, other bone marrow failure syndromes	2.2	2.4
Acquired hemolytic anemias	0.6	0.4

SOURCE: VA (2014a,b).

Conclusions

The new secondary studies of Gulf War veterans that compared cardiovascular disease in deployed veterans versus nondeployed veterans had mixed results. One study found that U.S. deployed veterans had a significantly increased risk of having tachycardia but a second study, using the same cohort, found no significant increase in the risk of having hypertension or of having coronary heart disease, although there was a moderate increase in the risk of developing both conditions. A study of Australian Gulf War veterans found no significantly increased risk of having high cholesterol, high blood pressure, heart attacks or myocardial infarction, or angina in deployed versus nondeployed veterans.

The committee finds that given the aging of the population of Gulf War veterans and the unlikelihood that new blood and circulatory conditions will develop 25 years after the Gulf war

that are attributable to their Gulf War service, it is doubtful that further assessments will show increased risk of these conditions.

Therefore, the Volume 10 committee concludes that there is inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and cardiovascular conditions or conditions of the blood organs.

TABLE 4-5 Conditions of the Blood and Circulatory System

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Volume 4 and 8 Primary Studies						
Cardiovascular System						
Eisen et al., 2005 (Vol. 4)	Population-based; cross-sectional; prevalence; medical evaluation; 1999–2001	1,061 U.S. GWVs and 1,128 NDVs	Hypertension = blood pressure > 140/90 mmHg or history of hypertension and use of antihypertensive medications	Hypertension: OR = 0.90 (95% CI 0.60–1.33)	Age, sex, race, years of education, smoking, duty type, service branch, rank	Low response rates, especially in control group (53% in GWVs, 39% in era controls), but analysis of nonparticipants and participants reveals no differences in hypertension or diabetes
Smith et al., 2003 (Vol. 4)	DoD hospitalization study (1991–2000); analysis of health outcomes and exposure to nerve agents	99,614 active-duty military considered exposed vs 318,458 nonexposed, according to revised DoD exposure model	First hospitalization for any disease of the circulatory system (ICD-9-CM codes 390–459); hospitalization for cardiac dysrhythmia	Circulatory system diseases: RR = 1.07 (95% CI 1.01–1.13); Cardiac dysrhythmia: RR = 1.23 (95% CI 1.04–1.44)	Sex, age, status, prewar hospitalization, pay grade, race, branch, days deployed, marital status, occupation	Restricted to DoD hospitals; restricted to hospitalizations for only Gulf War veterans who remained on active duty after the war; no adjustment for confounding exposures
Gray et al., 1996 (Vol. 8)	Retrospective cohort, hospitalizations from August 1991 through September 1993	547,076 active-duty GWVs and 618,335 NDVs	Hospital-discharge diagnoses of circulatory system disease in DoD hospital system (ICD-9 classification)	ORs about 0.90–0.95 (95% CI 0.85–1.05) across all 3 years, 1991–1993 Exact values not given	Prewar hospitalization, sex, age, race, service branch, marital status, rank, length of service, salary, occupation	Very short follow-up period; no outpatient data; restriction to DoD hospitals, and thus to persons remaining on active duty after the war; no adjustment for

Study	Design	Population	Outcomes	Results	Adjustments	Comments
						potential confounders such as smoking
Gray et al., 2000 (Vol. 8)	Retrospective cohort, hospitalizations from August 1991 through December 1994	652,979 GWVs, 652,922 randomly selected NDVs 182,164 DoD hospitalizations; 16,030 VA hospitalizations; 5,185 COSHPD hospitalizations	Hospital-discharge diagnoses of circulatory system disease in DoD, VA, and COSHPD hospital systems	Circulatory system disease: DoD PMR = 0.94 (95% CI 0.91–0.98); VA PMR = 0.85 (95% CI 0.76–0.93); COSHPD PMR = 0.98 (95% CI 0.82–1.14)	Age, sex, race (only for DoD PMR) Age, sex (for VA and COSHPD PMR)	Able to assess only illnesses that resulted in hospitalization; possible undetected confounders PMR has lower sensitivity than a comparison of hospitalization rates
Smith et al., 2002 (Vol. 8)	DoD hospitalizations 1991–1999; exposure modeling for smoke from oil-well fires	405,142 active-duty GWVs who were in theater during the time of Kuwaiti oil-well fires	Hospitalization for diseases of the circulatory system and for ischemic heart disease specifically	Significant decrease in risk ratio for exposed to oil-well fire smoke vs nonexposed in 3 of 5 exposure categories Lower risk of ischemic heart disease in all exposed vs nonexposed (RR = 0.82, 95% CI 0.68–0.99)	Adjusted for "influential covariates," defined as demographic or deployment variables with *p* values less than 0.15	Objective measure of disease not subject to recall bias; no issues with self-selection; however, only DoD hospitals, only active duty, no adjustment for potential confounders such as smoking
Smith et al., 2006 (Vol. 8)	Retrospective cohort study (cohort data from DMDC)	Active-duty personnel with a single deployment to: Gulf War theater (n = 455,465); Southwest Asia	Postdeployment hospitalization events (1991–2000) for an ICD-9-CM diagnosis of a disease of the circulatory system (390–459)	Compared to GWVs, veterans of Bosnia showed reduced risk (HR = 0.70, 95% CI 0.59–0.83), and veterans of Southwest Asia showed similar risk (HR = 1.06, 95% CI 0.97–1.16)	Sex, age, marital status, pay grade, race/ethnicity, service branch, occupation, and predeployment hospitalization;	Lower hazard ratio observed in veterans of Bosnia may be partially explained by shorter follow-up period Limitations: active-

Study	Design	Population	Outcomes	Results	Adjustments	Comments
		peacekeeping mission, 1991–1998 (n = 249,047); Bosnia, 1995–1998 (n = 44,341)			time-dependent covariate to account for changing hospitalization methods, diagnostic criteria, and procedures	duty personnel only; hospitalizations at DoD facilities only
Ishoy et al., 1999b (Vol. 8)	Cross-sectional	686 Danish peacekeepers deployed to gulf in 1990–1997 vs 231 age- and sex-matched nondeployed controls	Blood pressure measured by physician	Deployed vs nondeployed: Systolic: 127 (sd = 12) vs 126 (sd = 11) mmHg Diastolic: 78 (sd = 9) vs 76 (sd = 10) mmHg		Participation rate: 83.6% deployed, 57.8% nondeployed
Sim et al., 2003 (Vol. 8)	Cross-sectional, mailed questionnaire and clinical examination	1,371 male and 30 female Australian GWVs; 1,368 male and 32 female NDVs	Blood pressure measured by a physician	High-normal blood pressure, males: OR = 1.1 (95% CI 0.9–1.3) Hypertension, males: OR = 1.1 (95% CI 0.9–1.4); females: similar prevalence (3%) in both groups	Service type, rank, age, education, marital status	High participation in deployed veterans (male 81%, female 79%), but low participation in control group (male 57%, female 44%) possibly leading to participation bias
Blood and Blood-Forming Organs						
Gray et al., 1996 (Vol. 8)	Retrospective cohort, hospitalizations from August 1991 through September	547,076 active-duty GWVs, 618,335 NDVs	Hospital-discharge diagnoses of blood disease in DoD hospital system	Exact values not given 1991: OR about 0.9 (95% CI 0.8–1.05); 1992: OR about 1.1 (95% CI 1.0–1.2) 1993, OR about 1.05 (95% CI 0.9–1.15)	Prewar hospitalization, sex, age, race, service branch, marital status, rank, length of	Short follow-up period; no outpatient data; restriction to DoD hospitals and thus to persons

Study	Design	Population	Outcomes	Results	Adjustments	Comments
	1993				service, salary, occupation	remaining on active duty after the war; no adjustment for other potential confounders.
Gray et al., 2000 (Vol. 8)	Retrospective cohort, hospitalizations from August 1991 through December 1994	652,979 GWVs, 652,922 randomly selected NDVs 182,164 DoD hospitalizations; 16,030 VA hospitalizations; 5,185 COSHPD hospitalizations	Hospital-discharge diagnoses of blood disease in DoD, VA, and COSHPD hospital systems	DoD PMR = 1.08 (95% CI 0.97–1.19) VA PMR = 0.77 (95% CI 0.54–1.01) COSHPD PMR = 1.09 (95% CI 0.22–1.96)	Age, sex, race (only for DoD PMR)	Able to assess only illnesses that resulted in hospitalization; possible undetected confounders; PMR has lower sensitivity than a comparison of hospitalization rates
Smith et al., 2006 (Vol. 8)	Retrospective cohort study (cohort data from DMDC)	Active-duty personnel with a single deployment to: Gulf War theatre (n = 455,465); Southwest Asia peacekeeping mission, 1991–1998 (n = 249,047); Bosnia, 1995–1998 (n = 44,341)	Postdeployment hospitalization events (1991–2000) for an ICD-9-CM diagnosis of a disease of the blood (280–289)	Compared to GW veterans, veterans of Bosnia showed similar risk (HR = 0.93, 95% CI 0.80–1.07), as did veterans of Southwest Asia (HR = 0.93, 95% CI 0.75–1.15)	Sex, age, marital status, pay grade, race/ethnicity, service branch, occupation, and predeployment hospitalization; time-dependent covariate to account for changing hospitalization methods, diagnostic criteria, and procedures	Limitations: active-duty personnel only; hospitalizations at DoD facilities only

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Smith et al., 2002 (Vol. 4)	DoD hospitalizations 1991–1999; exposure modeling for smoke from oil-well fires	405,142 active-duty GWVs who were in theater during the time of Kuwaiti oil-well fires	Hospitalization for diseases of the blood (ICD-9-CM codes 280–289)	No clear association between exposure and blood disease across all exposure levels	Adjusted for "influential covariates," defined as demographic or deployment variables with *p* values less than 0.15	Objective measure of disease not subject to recall bias; no issues with self-selection; however, only DoD hospitals, only active duty, no adjustment for potential confounders such as smoking
Smith et al., 2003 (Vol. 4)	DoD hospitalization study (1991–2000); analysis of health outcomes and exposure to nerve agents (follow-up of Gray et al., 1999b)	99,614 active-duty military considered exposed vs 318,458 nonexposed, according to revised DoD exposure model	First hospitalization for any blood disorder (ICD-9-CM codes 280–289)	Exposed vs unexposed: RR = 0.96 (95% CI 0.89–1.03)	Sex, age, status, prewar hospitalization, pay grade, race, branch, days deployed, marital status, occupation	Restricted to DoD hospitals; restricted to hospitalizations for only Gulf War veterans who remained on active duty after the war; no adjustment for confounding exposures
Ishoy et al., 1999b (Vol. 8)	Cross-sectional	686 Danish peacekeepers deployed to gulf in 1990–1997 vs 231 age- and sex- matched nondeployed controls	Blood hemoglobin, erythrocyte count, hematocrit, mean corpuscular volume, leukocyte count, and platelet count	Hemoglobin (mmol/L): 9.3 (sd = 0.5) vs 9.3 (sd = 0.6); erythrocytes (million/L): 4.8 (sd = 0.3) vs 4.8 (sd = 0.3); hematocrit 0.44 (sd = 0.25) vs 0.44 (sd = 0.26); corpuscular volume (10–15 L): 91 (sd = 3.6) vs 91 (sd = 3.8); leukocytes (10^9/L): 5.8 (1.7) vs 5.9 (sd = 1.8); platelets (10^9/L): 205 (sd = 45) vs 211 (sd = 43), $p < 0.05$	None	Participation rate: 83.6% deployed, 57.8% nondeployed; no adjustment for possible confounding factors

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Sim et al., 2003 (Vol. 8)	Cross-sectional, mailed questionnaire and clinical examination	1,355 male and 30 female Australian GWVs; 1,361 male and 32 female nondeployed veterans	Hemoglobin, MCV, MCH, lymphocyte count, platelet count	Hemoglobin (g/L), men: 153.4 (sd = 9.5) vs 153.1 (sd = 9.1); women: 131.8 vs 134.3 MCV (fl), men: 91.6 (sd = 4.7) vs 91.5 (sd = 4.5); women: 92.8 vs 93.4 MCH (pg), men: 30.4 (sd = 1.4) vs 30.5 (sd = 1.3); women: 29.8 vs 30.3 Lymphocyte count (10^9/L), men: 1.9 (sd = 0.5) vs 1.9 (sd = 0.6); women: 2.0 vs 2.1 Platelets (10^9/L), men: 227.8 (sd = 44.4) vs 231.3 (sd = 48.5); women: 263.6 vs 269.6	Service type, rank, age, education, marital status	High participation in deployed veterans (male 81%, female 79%), but low participation in control group (male 57%, female 44%) possibly leading to participation bias

NOTE: CI = confidence interval; COSHPD = California Office of Statewide Health Planning and Development; DMDC = Defense Manpower Data Center; DoD = Department of Defense; GW = Gulf War; GWV = Gulf War veteran; HR = hazard ratio; ICD = International Classification of Diseases; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; mmHg = millimeters of mercury; mmol = millimoles; NDV = nondeployed veteran; OR = odds ratio; pg = picogram; PMR = proportional morbidity ratio; RR = risk ratio; sd = standard deviation; VA = Department of Veterans Affairs.

ENDOCRINE AND METABOLIC CONDITIONS

Among the general U.S. population, the most frequent conditions in this category are diabetes, thyroid disease, and obesity. It is estimated that 29 million people in the United States (9.3%) have diabetes; 1.7 million people aged 20 years or older were newly diagnosed with diabetes in 2012, and another 86 million adults—more than one in three U.S. adults—have prediabetes, where their blood sugar levels are higher than normal but not high enough to be classified as type 2 diabetes (CDC, 2015a). The CDC also estimates that more than one-third (34.9% or 78.6 million) of U.S. adults are obese (CDC, 2015b), a risk factor for diabetes. Although the Volume 10 committee attempted to identify other specific endocrine or metabolic conditions in Gulf War veterans, no new literature on those outcomes was found to have been published since Volume 8. Primary studies for Volumes 4 and 8 are detailed in Table 4-7 at the end of this section.

Summary of Volumes 4 and 8

Volume 4 included diabetes under diseases of the circulatory system. Two primary studies were identified; one study (Eisen et al., 2005) included medical evaluations for diabetes, and the other (Smith et al., 2003), a hospitalization study, used a dispersion model to determine exposure status to nerve agents at the Khamisiyah demolition site. Neither study found a statistically significant increase in the prevalence of diabetes in deployed veterans or in hospital diagnoses for endocrine, nutritional, and metabolic diseases. None of the four secondary studies found a statistically significant increase in diabetes in any of the Gulf War veteran populations they studied; however, most of the studies relied on self-reported diagnoses.

Two primary studies reviewed by the Volume 8 committee reported on risk factors of diabetes, insulin levels, and blood glucose in Gulf War veterans from Denmark (Ishoy et al., 1999b) and Australia (Sim et al., 2003), but neither reported differences between deployed and nondeployed veterans. The five secondary studies of self-reported outcomes in four military cohorts indicated comparable risks of diabetes between deployed and nondeployed veterans (Simmons et al., 2004; Kang et al., 2009; Page et al., 2005a; Proctor et al., 2001a; Smith et al., 2006).

Thyroid disease was not specifically described in Volume 4. The Volume 8 committee reviewed one primary study (Eisen et al., 2005) that reported elevated but not statistically significant risks for hyperthyroidism and for hypothyroidism in deployed veterans compared with nondeployed veterans based on medical examinations.

Obesity was also not studied separately in Volume 4. Studies reviewed by the Volume 8 committee used measures of BMI, weight, and waist circumference to measure obesity in veterans. One primary study, conducted in 1997, found a slightly higher weight and waist circumference in Danish deployed veterans compared with nondeployed veterans (Ishoy et al., 1999b), whereas an Australian study found that BMI and waist circumference measures were comparable between deployed and nondeployed male and female veterans in 2002 (Sim et al., 2003). A secondary study found no differences in BMI, glycemia, or blood levels of thyroxine-stimulating hormone between deployed and nondeployed UK veterans (Ismail et al., 2008).

The Volume 8 committee reported that primary studies showed no clinically relevant differences between deployed and nondeployed veterans in prevalence of different endocrine and

metabolic conditions, including diabetes, thyroid disease, and obesity. Five of the eight primary studies relied on hospital discharge data; thus, conditions that did not require hospitalization were not evaluated. The existing studies, however, did not indicate any increased risk of these conditions among deployed veterans. Results from secondary studies were similarly inconclusive: deployment status was unrelated to self-reported diabetes but observed findings were less consistent for other endocrine disorders. *The Volume 8 committee concluded that there was inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and endocrine, nutritional, and metabolic conditions.*

New Literature

No new primary studies were identified by the Volume 10 committee.

Secondary Studies

The Volume 10 committee identified three studies that met its criteria for secondary studies. These studies assessed the prevalence of diabetes on the basis of self-reports.

Li et al. (2011a) conducted a 10-year follow-up survey of U.S. Gulf War deployed (n = 5,469) and nondeployed veterans (n = 3,353) who had participated in the 1995 VA National Health Survey. Compared with nondeployed veterans, deployed veterans in 2005 were at decreased risk of having diabetes (RR = 0.8, 95% CI 0.7–1.0) or having new onset of the disease (RR = 0.9, 95% CI 0.8–1.2). The risk ratios were adjusted for age in 2005, gender, race, rank, service branch, service type, BMI, and current cigarette smoking.

Sim et al. (2015) conducted the Australian Gulf War Veterans' Follow-Up Health Study between 2011 and 2013 to assess the entire Australian Gulf War cohort 10 years after the 2000–2002 baseline study and 20 years after the war. Results were adjusted for age, rank category, and service branch, but not for smoking. Of the 1,456 eligible deployed veterans, 715 participated in the study and 675 of the 1,449 nondeployed veterans provided the comparison group. Health outcomes were based on self-reports and on self-reports of doctor-diagnosed diseases. Deployed veterans had a nonsignificant decreased risk of having diabetes compared with nondeployed veterans (RR = 0.76, 95% CI 0.51–1.14).

Dursa et al. (2016) reported results from the third wave of the cross-sectional National Health Study of Persian Gulf War Era Veterans that was conducted in 2012–2013 and asked 8,104 deployed and 6,148 Gulf War era veterans whether a doctor ever told the veteran that they had diabetes or some other endocrine disorder. The weighted prevalence for diabetes was the same in deployed and era veterans—13.2%, but the OR was not statistically significant. Era veterans had a slightly higher weighted prevalence (8.0%) of other endocrine disorders compared with deployed veterans (7.4%), but the OR of 1.09 was not statistically significant (95% CI 0.87–1.33).

Other Related Studies

Other studies have assessed the effect of a co-occurring health condition on the prevalence of diabetes and other endocrine and metabolic conditions. In a 2003–2005 follow-up to the 1995 National Health Survey of Gulf War Veterans and Their Families, Coughlin and colleagues (2011a) investigated self-reported health outcomes among 6,111 Gulf War deployed and 3,859 era veterans stratified by weight. The percentage of normal weight, overweight, and obese deployed veterans who reported a diagnosis of diabetes was 9%, 10.8%, and17.5%, respectively. The corresponding percentages for nondeployed veterans were 7.8%, 10.1%, and

15.6%, respectively. Underweight deployed and nondeployed veterans had a greater percentage of diabetes than normal weight veterans (15.4% and 16.7%, respectively). These data were not adjusted for age and no information on diet or physical activity was provided in this study.

VA provided a health care use report for Gulf War deployed and era veterans who sought care in VA facilities from October 2001 to December 2013. The report presented the prevalence of diagnoses of diseases by ICD-9 code categories, including for diseases of the endocrine, nutritional, and metabolic systems (ICD-9-CM 240-279) (Table 4-8); no statistical analyses were performed. A veteran can have multiple diagnoses with each health care encounter, and therefore, may be counted in multiple categories, but the veteran is counted only once in any single diagnostic category. A total of 286,995 Gulf War deployed and 296,635 era veterans received treatment at VA over the approximately 11-year period (VA, 2014a,b). These VA health care users represent 46% of all deployed Gulf War veterans and 36% of all nondeployed era veterans.

TABLE 4-8 Ten Most Frequent Diagnoses of Diseases of the Endocrine, Nutritional, and Metabolic Systems for Deployed and Nondeployed Gulf War Veterans Seeking Health Care in VA Between 2002 and 2013

Diagnosis	Deployed N = 28,305 (%)	Nondeployed N = 28,307 (%)
Disorders of lipid metabolism	76.8	76.4
Overweight, obesity, other hyperalimentation	45.1	46.1
Diabetes mellitus	25.9	24.6
Vitamin D deficiency	9.0	9.0
Disorders of fluid, electrolyte, acid–base balance	8.5	8.0
Acquired hypothyroidism	8.4	7.1
Gout	6.6	6.6
Testicular dysfunction	4.7	5.1
Deficiency of B-complex components	2.7	2.6
Disorders of mineral metabolism	2.4	2.3

SOURCE: VA (2014a,b).

Conclusions

The Volumes 4 and 8 committees found no evidence of an increase in the prevalence of endocrine disorders such as diabetes and thyroid disease or disorders such as obesity in veterans who were deployed to the Gulf War. The several hospitalization studies also found no increased risk of these conditions, although the Volume 8 committee noted that most of these conditions do not require hospitalization and therefore, the prevalence may be underreported. The new literature reviewed by the Volume 10 committee, much of which was follow-up of previously discussed Gulf War veteran cohorts, also found no evidence of an increased risk of having or developing diabetes or other endocrine or metabolic conditions.

The committee finds that given the aging of the population of Gulf War veterans and the unlikelihood that new endocrine and metabolic conditions will develop 25 years after the Gulf war that are attributable to their Gulf War service, it is doubtful that further assessments will show an increased risk of these conditions.

Therefore, the Volume 10 committee concludes that there is inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and endocrine and metabolic conditions.

TABLE 4-7 Conditions of the Endocrine and Metabolic Systems

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Eisen et al., 2005 (Vol. 4)	Cross-sectional, prevalence, population-based (derived from Kang et al., 2000b)	1,061 GWVs and 1,128 NDVs	Diabetes, hypothyroidism, hyperthyroidism	Diabetes (OR = 1.52, 95% CI 0.81–2.85); hypothyroidism (OR = 1.70, 95% CI 0.75–3.87); hyperthyroidism (OR = 4.86, 95% CI 0.68–34.58); no outcomes tested were significant	Age, sex, race, smoking, duty type, service branch, education, rank (hyperthyroidism not adjusted for service branch or rank)	Low participation rates, deployed (53%), nondeployed (39%)
Smith et al., 2003 (Vol. 4)	DoD hospitalization study (1991–2000) of those potentially exposed to nerve agent	99,614 active-duty military considered exposed vs 318,458 nonexposed, according to revised DoD exposure model	Hospitalization due to endocrine, nutritional, and metabolic diseases (ICD-9 classification)	RR = 1.00 (95% CI 0.94–1.06)	One or more hospitalizations in a specific diagnostic category	Diagnoses not requiring hospitalization not captured; no outpatient data; DoD hospitals and active duty only; not possible to adjust for confounding exposures
Ishoy et al., 1999b (Vol. 8)	Cross-sectional	686 Danish peacekeepers deployed to gulf in 1990–1997 vs 231 age- and sex-matched nondeployed controls	Plasma insulin levels Avg. weight and waist circumference	No significant difference in insulin levels between deployed (48 pmol/L) and nondeployed (52 pmol/L) Weight and waistline were higher ($p < 0.05$) for deployed (84.2 kg, 90.2 cm) than for nondeployed (81.9 kg, 88.3 cm)		Participation rate: 83.6% deployed, 57.8% nondeployed

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Sim et al., 2003 (Vol. 8)	Cross-sectional, mailed questionnaire and clinical examination	1,384 male and 30 female Australian GWVs; 1379 male and 32 female NDVs (Only 1,365 GWVs and 1,365 NDVs for plasma glucose analysis)	Plasma glucose; BMI; waist circumference	Plasma glucose, men: 85 mg/dL in both groups; women: 90 mg/dL vs 81 mg/dL BMI, men: 28.1 kg/m2 (sd = 4.1) vs 28.3 kg/m2 (sd = 4.1), OR = -0.3 (95% CI -0.6–0.02); women: 26 kg/m2 in both groups Waist circumference, men: 97.7 cm (sd = 10.7) vs 98.2 cm (sd = 10.7), OR = -0.6 (95% CI -1.4–0.2) ; women: 86.3 cm vs 83.4 cm	Service type, rank, age (< 20, 20-24, 25 to 34, ≥ 35 years), education and marital status	High participation in deployed veterans (male 81%, female 79%), but low participation in control group (male 57%, female 44%) possibly leading to participation bias
Smith et al., 2003 (Vol. 4)	DoD hospitalization study (1991–2000); analysis of health outcomes and exposure to nerve agents (follow-up of Gray et al., 1999b)	99,614 active-duty military considered exposed vs 318,458 nonexposed, according to revised DoD exposure model	First hospitalization for any endocrine, nutritional, and metabolic diseases (ICD-9-CM codes 240–279)	Exposed vs unexposed: RR = 1.00 (95% CI 0.94–1.06)		Restricted to DoD hospitals; restricted to hospitalizations for only GWVs who remained on active duty after the war; no adjustment for confounding exposures; diagnoses not severe enough to require hospitalization are not captured

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Gray et al., 1996 (Vol. 8)	Retrospective cohort, hospitalizations from August 1991 through September 1993	547,076 active-duty GWVs, 618,335 NDVs	Hospital-discharge diagnoses of endocrine, metabolic, or nutritional system diseases in the DoD hospital system (ICD-9 classification)	OR about 0.85–0.90 (95% CI 0.80–0.95) across all three years, 1991–1993, exact values not given	Prewar hospitalization, sex, age, race, branch of service, marital status, rank, length of service, salary, occupation	Very short follow-up period; no outpatient data; restriction to DoD hospitals, and thus to persons remaining on active duty after the war; no adjustment for potential confounders
Gray et al., 2000 (Vol. 8)	Retrospective cohort, hospitalizations from August 1991 through December 1994	652,979 GWVs, 652,922 randomly selected NDVs 182,164 DoD hospitalizations; 16,030 VA hospitalizations; 5185 COSHPD hospitalizations	Hospital-discharge diagnoses for endocrine, nutritional, and metabolic disease in three hospital systems: DoD, VA, COSHPD	DoD PMR = 0.99 (95% CI 0.93–1.06) VA PMR = 1.08 (95% CI 0.92–1.24) COSHPD PMR = 0.81 (95% CI 0.48–1.14)	Age, sex, race (only for DoD PMR)	Able to assess only illnesses that resulted in hospitalization; possible undetected confounders PMR has lower sensitivity than a comparison of hospitalization rates
Smith et al., 2002 (Vol. 8)	DoD hospitalizations 1991–1999; exposure modeling for smoke from oil-well fires	405,142 active-duty GWVs who were in theater during the time of Kuwaiti oil-well fires	Association of exposure level with hospitalizations for endocrine, nutritional, and metabolic disease (ICD-9 classification)	No significant difference between RR for exposure at any level vs nonexposed	Adjusted for "influential covariates", defined as demographic or deployment variables with *p* values less than 0.15	Objective measure of disease not subject to recall bias; no issues with self-selection; however, only DoD hospitals, only active duty, no adjustment for potential confounders such as smoking
Smith et al., 2006 (Vol. 8)	Retrospective cohort study	Active-duty personnel with a single deployment to:	Postdeployment hospitalization events (1991–2000) for an ICD-9-CM	Veterans of Bosnia, HR = 0.69 (95% CI 0.57–0.84) Veterans of SW Asia,	Sex, age, marital status, pay grade, race/ethnicity, service branch, occupation,	Limitations: active-duty personnel only; hospitalizations at DoD facilities only

Study	Design	Population	Outcomes	Results	Adjustments	Comments
		Gulf War theater (n = 455,465); Southwest Asia peacekeeping mission, 1991–1998 (n = 249,047); Bosnia, 1995–1998 (n = 44,341)	diagnosis of an endocrine disease (240–279)	HR = 1.02 (95% CI 0.92–1.13)	and predeployment hospitalization; time-dependent covariate to account for changing hospitalization methods, diagnostic criteria, and procedures	

NOTE: BMI = body mass index; CI = confidence interval; COSHPD = California Office of Statewide Health Planning and Development; DoD = Department of Defense; GWV = Gulf War veterans; HR = hazard ratio; ICD = International Classification of Diseases; NDV = nondeployed veterans; OR = odds ratio; pmol = picomoles; PMR = proportional morbidity ratio; RR = risk ratio; VA = Department of Veterans Affairs.

MENTAL AND BEHAVIORAL HEALTH CONDITIONS

Mental health disorders are among the most disabling and costly health conditions globally. Notwithstanding their high prevalence and their impact on cost and disability, appropriate interventions for mental health conditions remain one of the most neglected areas in health care worldwide, a reality that may be related to stigma as well as diagnostic issues. The latter may result in ambiguous definitions that may affect the proper characterization of those in need of services.

Mental health conditions are well-known sequelae of war (Pizarro et al., 2006; Wessely, 2005). These conditions have been an important focus of studies of military populations, and each large cohort study of Gulf War veterans has included at least some psychological assessments. Mental health conditions most commonly studied in the Gulf War veteran population include major depression disorder (MDD), PTSD, and substance use disorders. In general, for most of the studies discussed in this section, the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual of Mental Health Disorders*, fourth edition (DSM-IV), was the basis for the assessment of mental health disorders in veterans and others.

In 2013, the APA released a revised fifth edition of the *DSM*, which substantially changed many of the criteria that are used to diagnose mental health disorders. For example, the *DSM-5* diagnostic criteria for PTSD may affect the incidence and prevalence of PTSD in both military and civilian populations. Part of the difficulty in assessing and treating for PTSD is the inherent heterogeneity in presentation. For example, Galatzer-Levy and Bryant (2013) found that the *DSM-5* criteria could result in 636,120 PTSD symptom combinations. The new criteria for PTSD are summarized in Box 4-1. None of the studies considered in this report used the new criteria.

General population estimates of prevalence of mental health conditions show that in general, about one-third of the U.S. adult population may, at some time in their lives, meet criteria for a mental health disorder. The National Comorbidity Survey–Replication, a large epidemiologic study in the United States, found a 12-month prevalence estimate of 3.1% for alcohol abuse, 2.4% for bipolar disorder, 1.4% for drug abuse, 2.7% for generalized anxiety disorder, 3.6% for PTSD, 8.9% for MDD, 3.7% for panic disorder, 7.2% for social phobia, and 9.2% for specific phobia (Gadermann et al., 2012). Lifetime prevalence for the same mental health disorders in the general U.S. population tends to be higher (Kessler et al., 2005). The rates of mental disorders in the general population based on the above estimates tend to be higher than those reported in deployed veterans and much higher than in the nondeployed veteran populations (IOM, 2010), a finding that has been interpreted as due to a "healthy-warrior effect," but these rates may not be comparable as they have been obtained through different research strategies. It is likely that both military screening and self-selection contribute to the belief that individuals entering the military, and being eligible for deployment, may have a better mental and physical health status than similar individuals in the general population. However, it is well recognized that deployment and exposure to combat result in an increased incidence of certain mental health disorders such as PTSD.

The proper examination of mental health conditions among veterans serving in the Gulf War has been complicated by the passage of time, the stigma that mental health disorders may convey on veterans and their families, and the rejection of these diagnoses by many veterans who

vigorously advocate against their symptoms and disorders being called "mental" or "psychiatric." Indeed, many Gulf War veterans fear that discussion of the psychological aspects of their symptoms would question the legitimacy of their health problems.

All primary studies of mental and behavioral health conditions are summarized in Table 4-9 at the end of this section.

Box 4-1
Revised Diagnostic Criteria for PTSD

In 2013, the American Psychiatric Association released the *DSM-5*, which included major revisions to the diagnostic criteria for PTSD and acute stress disorder. Both of these disorders are now categorized as "trauma- and stressor-related disorders," rather than as anxiety disorders. The 17 PTSD symptoms from the *DSM-IV-TR* remain, and three new ones have been added. The definition of a "traumatic event" was further clarified to include exposure to actual or threatened death, serious injury, or sexual violation, as directly experienced or experienced through repeated or extreme exposure to aversive details of the traumatic event, witnessed, or (for traumatic events occurring to close family members or friends) learned about by a person. The person must experience clinically significant distress or functional impairment related to the event, but the former criterion that the person's response to a traumatic event had to involve intense fear, helplessness, or horror has been removed. Criterion B remains unchanged and covers symptoms of re-experiencing, Criterion C has been shortened and contains symptoms of avoidance, and Criterion D has been added to encompass symptoms related to negative cognitions and mood. *DSM-5* requires that the symptoms continue for more than a month and no longer distinguishes between acute and chronic phases of PTSD. Two subtypes of PTSD have been added: a clinical subtype with prominent dissociative symptoms for people who, in addition to meeting the criteria for PTSD, experience depersonalization and derealization symptoms, and PTSD in children 6 years old and younger.

SOURCE: APA (2013).

Summary of Volumes 4 and 8

In Volume 4, eight primary studies were reviewed that used direct interviews of the large Gulf War cohorts. Across those studies, publications from three U.S. cohorts, one Australian cohort, and one Canadian cohort reported a 2- to 3-fold increased prevalence of mental health conditions including generalized anxiety disorder, panic disorder, PTSD, any anxiety disorder, and substance abuse in deployed versus nondeployed veterans (Barrett et al., 2002; Black et al., 2004a,b; Brailey et al., 1998; Kang et al., 2003; Proctor et al., 1998; Wolfe et al., 1999a,b;). Analyses also indicated reduced functioning and quality of life in deployed veterans with mental health conditions. Two of those studies indicated that symptoms of depression and PTSD could worsen over time (Brailey et al., 1998; Wolfe et al., 1999a). The primary studies and most of the secondary studies, regardless of their techniques of ascertainment or their target population, reported almost identical conclusions regarding the psychiatric outcomes of Gulf War deployment for veterans. Depression, substance abuse or dependence, and anxiety disorders, especially PTSD, were increased in Gulf War deployed veterans compared with nondeployed veterans. Symptom severity was associated with the perceived level of deployment stress, even if veterans did not have direct combat exposure.

The Volume 8 committee identified four new primary studies (Fielder et al., 2006; Ismail et al., 2002; Kang et al., 2009; Toomey et al., 2007) and five new secondary studies (Al-Turkait and Ohaeri, 2008; Axelrod et al., 2005; Black et al., 2006; Kang et al., 2005; Rona et al., 2007) that further supported the Volume 4 committee conclusions on the relationship between deployment to the Gulf War and mental health disorders. First, that committee found that combat exposure in the Gulf War was causally related to PTSD. The primary studies were in U.S., UK, and Kuwaiti veterans. The available evidence from these studies is sufficient to support the conclusion that the causal relationship of combat exposure to PTSD shown for other wars, such as Vietnam and the conflicts in Iraq and Afghanistan, also pertains to combat exposure and the development of PTSD in the 1990–1991 Gulf War. Second, there is sufficient evidence of an association between deployment to the Gulf War and several other psychiatric disorders. These include generalized anxiety disorder, depression, and substance abuse, particularly alcohol abuse. Third, the associations between Gulf War deployment and psychiatric disorders were still evident 10 years after deployment. For many of the psychiatric disorders that were measured in long-term follow-up studies, their prevalence even 10 years after the war was more than two-fold higher in veterans who had been deployed compared with nondeployed veterans.

In particular, the Volume 8 committee found that the high prevalence of medically unexplained disability in Gulf War veterans could not be completely explained by specific psychiatric causes or disorders. Somatization disorder, which is rare, requires eight symptoms that are not caused by a medical illness. Somatoform disorders in *DSM-IV* included separate diagnoses such as somatization disorder, hypochondriasis, pain disorder, and undifferentiated somatoform disorder. The latter is a disorder with little specificity and is by far the most commonly found; it requires only one symptom that cannot be attributed to known medical causes. In the study by Ismail et al. (2002), "undifferentiated somatoform disorder" was more commonly seen in deployed than in nondeployed Gulf War veterans and in disabled Gulf War veterans compared with disabled veterans from other wars, but the diagnosis was present in only a small minority of disabled Gulf War veterans, and medical evaluations were not sufficiently comprehensive to rule out medical explanations for the symptoms in those given the undifferentiated somatoform disorder diagnosis. Fiedler et al. (2006) and Toomey et al. (2007) found almost no cases of somatization disorder among Gulf War veterans, nor was there a significant elevation in somatization disorder among deployed versus nondeployed veterans. They and other researchers (Toomey et al., 2007; Al-Turkait and Ohaeri, 2008) found a statistically significant increase in the prevalence of psychiatric disorders, notably PTSD, MDD, and substance dependence, in deployed versus nondeployed Gulf War veterans. Thus, based on available evidence that used the *DSM-IV* for diagnoses, the high prevalence of medically unexplained disability in Gulf War veterans cannot be explained by *DSM-IV* somatoform disorders.

On the basis of available evidence, the Volume 8 committee concluded that there was sufficient evidence of a causal relationship between traumatic war exposures experienced during deployment to the Gulf War and PTSD. The committee also concluded that there was sufficient evidence of an association between deployment to the Gulf War and other psychiatric disorders, including generalized anxiety disorder, depression, and substance abuse, particularly alcohol abuse. Furthermore, these disorders persist for at least 10 years after deployment. Finally, the excess of unexplained medical symptoms reported by deployed Gulf war veterans cannot be fully explained by any DSM-IV *psychiatric disorder.*

New Literature

Primary Studies

During its review of the scientific literature on mental health disorders in Gulf War veterans published since 2008, the committee identified only one new study that met its criteria for a primary study (Sim et al. 2015). The Australian-based Gulf War Veterans' Follow Up Health Study, conducted between 2011 and 2013, is an assessment of the entire 1,871 Australian Gulf War cohort 10 years after the 2000–2002 baseline study and 20 years after the war (Sim et al., 2015). Because only about 2% of the participants were women, only males were recruited for the study. Results were adjusted for age, rank category, and service branch. Of the deployed cohort of 1,456 eligible veterans, 715 participated in the study and 675 of the 1,449 nondeployed veterans provided the comparison group. There were four survey components (see Chapter 3), one of which—the CIDI, administered via telephone—was used to assess the presence of mental health disorders. Based on the CIDI interviews, as well as responses to the Posttraumatic Stress Disorder Checklist (PCL) and self-reports of doctor-diagnosed and treated PTSD in the past 12 months, 7.3% (PCL) and 8.2% (CIDI) of the deployed veterans met the criteria for PTSD compared with 2.7% (PCL) and 4.8% (CIDI) of the nondeployed veterans. Compared with the prevalence of PTSD in the baseline study, deployed veterans were more likely to have PTSD in the follow-up (RR = 1.96, 95% CI 1.29–2.97). Furthermore, Gulf War veterans were more likely to develop incident PTSD than nondeployed veterans (RR = 2.29, 95% CI 1.24–4.24). The authors report that excess PTSD in Gulf War veterans appears to persist even 20 years after the war, and it appears to be increasing with time compared with the nondeployed veterans.

Sim et al. (2015) also used the CIDI to assess for other mental health disorders in the Australian veterans between 2011 and 2013. Compared with nondeployed veterans, deployed veterans had a greater risk for 12-month alcohol use disorder at follow-up (RR = 1.93, 95% CI 1.10–3.38) or the AUDIT (RR = 1.26, 95% CI 1.05–1.52), but not self-reported doctor diagnosis and treatment (RR = 1.55, 95% CI 0.64–2.81). The prevalence of alcohol use disorder had about doubled in deployed veterans since the baseline study (RR = 2.0, 95% CI 1.25–3.20); a similar increase in nondeployed veterans was not statistically significant (RR = 1.78, 95% CI 0.84–3.76). The number of substance use disorders was too small to allow for statistical analysis and was not assessed. There were no statistically significant differences between the Gulf War and era veterans in the prevalence of other 12-month mental health disorders (as measured by the CIDI) including dysthymia, bipolar disorder, generalized anxiety disorder, obsessive compulsive disorder, social phobia, specific phobia, panic disorder, drug dependence or abuse, and any somatic disorder (i.e., somatization, conversion disorder, pain disorder, and hypochondriasis).

Compared with PTSD and alcohol use disorders, the prevalence of major depressive disorder did not differ between the two groups at follow-up (RR = 1.2, 95% CI 0.8–1.7), although it had increased by about 2% in each group since the baseline assessment (from 7.8% to 9.6% in deployed and from 5.0% to 7.2% in nondeployed veterans) (Sim et al., 2015). In a separate analysis of the depression data, it was noted that deployed veterans reported slightly more severe symptoms and were more likely to have been prescribed antidepressants (RR = 1.56, 95% CI 1.05–2.32). There was also a dose–response relationship between depression and self-reports of war-related stressors (Ikin et al., 2015).

Sim et al. (2015) also reported that one out of four Gulf War veterans and one out of six comparison group participants met the criteria for at least one CIDI-defined 12-month psychiatric disorder at follow-up. This difference between groups was statistically significant.

Secondary Studies

The committee identified two studies published in the peer-reviewed literature that met its criteria for a secondary study. In 1997, Ishoy et al. (2004) examined psychological symptoms in 686 Danish Gulf War veterans and 231 nondeployed military controls who were matched to the deployed veterans on age, gender, and profession. Subjects completed the Symptom Check List, revised edition (SCL-90-R), that measures self-reports of symptoms of psychological distress in nine dimensions: somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobia, paranoid ideation, and psychoticism. Being a Gulf War veteran was statistically significantly associated with six of the nine dimensions—somatization, interpersonal sensitivity, anxiety, hostility; the strongest associations were with obsessive-compulsive and depression. The associations with phobia, paranoid ideation, and psychoticism were not significant.

In addition to the published study by Ishoy et al. (2004), Dursa et al. (2016) published on the most recent results of the third survey wave of the cross-sectional National Health Study of Persian Gulf War Era Veterans. The wave 3 survey (discussed in greater detail in Chapter 3), conducted in 2012–2013, asked 8,104 deployed and 6,148 Gulf War era veterans to indicate whether a doctor had ever told them they had a medical condition and then whether the condition had been present in the previous 4 weeks. Depression and alcohol use are included in the survey, and participants were also asked about the effect of a variety of emotional problems on their daily lives. The 17-question PCL was used to screen for PTSD. After adjustment for age, race, sex, service branch, and unit component, the adjusted OR for a positive screen for a mental health condition for deployed versus era veterans was 1.93 (95% CI 1.67–2.24) for PTSD, 1.56 (95% CI 1.41–1.73) for MDD, 1.24 (95% CI 1.08–1.38) for other depressive disorders, and 1.34 (95% CI 1.17–1.54) for other anxiety disorders.

Other Related Studies

Blore et al. (2015) reviewed 14 studies that compared the presence of depression and dysthymia or chronic dysphoria in Gulf War veterans with nondeployed veterans (11 of the studies were discussed in Volumes 4 or 8). The authors concluded that although PTSD has been the focus of attention in past studies, depression and dysthymia were twice as common among Gulf War veterans compared to nondeployed military personnel (OR = 2.28, 95% CI 1.88–2.76 and OR = 2.39, 95% CI 2.0–2.86, respectively), regardless of the method used to screen for or diagnose the disorders.

VA provided a health care use report for Gulf War deployed and era veterans who sought care in VA facilities from October 2001 to December 2013. The report presented the prevalence of diagnoses of diseases by ICD-9 code categories, including mental health diagnoses (ICD-9-CM 290–319) (Table 4-10). A veteran can have multiple diagnoses with each health care encounter, and therefore, may be counted in multiple categories, but the veteran is counted only once in any single diagnostic category. A total of 286,995 Gulf War deployed and 296,635 era veterans received treatment at VA over the approximately 11-year period (VA, 2014a,b). These VA health care users represent 46% of all deployed Gulf War veterans and 36% of all nondeployed era veterans.

TABLE 4-10 Ten Most Frequent Mental Health Diagnoses for Deployed and Nondeployed Gulf War Veterans Seeking Health Care in VA Between 2002 and 2013

Diagnosis	Deployed N = 157,277 (%)	Nondeployed N = 129.561 (%)
Adjustment reaction	52.4	39.5
Nondependent abuse of drugs	51.0	49.5
Depressive disorder NEC	48.5	46.1
Anxiety, dissociative, somatoform disorders	37.9	35.3
Episodic mood disorder	30.6	29.6
Alcohol dependence syndrome	16.8	14.7
Sexual, gender identity disorders	15.5	16.7
Drug dependence	9.8	8.8
Special symptoms or syndromes, NEC	8.9	8.1
Personality disorders	5.3	Not reported

NOTE: NEC = not elsewhere classified.
SOURCE: VA (2014a,b).

The prevalence of PTSD specifically in U.S. Gulf War veterans has been the subject of a systematic review and meta-analysis by Magruder and Yeager (2009). Using quality adjusted Forrest plots of 12 papers published between 1993 and 2003 that assessed PTSD in deployed and nondeployed veterans (one paper was on women veterans only), the authors found that deployed veterans were twice as likely to develop PTSD as were nondeployed veterans (overall OR = 2.03, 95% CI 1.32–3.15; OR range for the 12 papers was 0.74–5.98). Studies were adjusted for sampling methods, sampling frame and study population, PTSD diagnostic criteria, time since exposure, survey methods, exposure assessment, participation rate, analytic strategy, and interviewer training. A similar meta-analysis was done by Kelsall et al. (2015) looking at literature published on Gulf War veterans between 1990 and 2014. They found seven studies that looked at alcohol use disorders in deployed and nondeployed Gulf War veterans and determined a summary OR of 1.33 (95% CI 1.22–1.46). The three studies that assessed substance use disorders in Gulf War veterans yielded an OR of 2.13 (95% CI 1.11–1.66). Kelsall et al. derived ORs for any studies that did not include them. All of the studies in these meta-analyses had been reviewed by the Volume 8 committee.

Although there were few papers that provided any evidence on which to reconsider the conclusions of the Volume 8 committee, this committee did identify several papers that contained findings that may inform future research efforts. For example, in a study of 1,197 male Royal Australian Navy veterans who had served in Gulf War, McKenzie et al. (2010) found that in veterans with no prewar history of mental health diagnoses, postdeployment diagnoses of alcohol abuse or dependence, anxiety disorders, and affective disorders peaked in the first 2 years after deployment, but then decreased in subsequent years. Alcohol abuse and dependence was the most prevalent diagnosis, and was greatest in veterans reporting the most psychological stressors, but anxiety disorders were the first to be evident. Although the onset of affective disorders also peaked at 1–2 years after the war, the effect of time phase was not significant.

In a 2003–2005 follow-up to the 1995 National Health Survey of Gulf War Veterans and Their Families, Coughlin et al. (2011a) found that PTSD was more prevalent in both deployed

and era Gulf War veterans who were obese or overweight compared with Gulf War veterans who were of normal weight (OR = 1.5, 95% CI 1.2–1.8 and OR = 1.2, 95% CI 1.0–1.5, respectively). These same researchers also found that when deployed veterans who had drinking problems were compared with deployed veterans who did not have drinking problems, the former were more likely to have PTSD (OR = 2.72, 95% CI 2.33–3.16) and MDD (OR = 2.32, 95% CI 1.99–2.70). PTSD and MDD were also more prevalent in nondeployed veterans with drinking problems (Coughlin et al., 2011b). Heavy drinking was defined as ≥ 15 drinks per week.

Previous IOM Gulf War and Health committees have found that veterans exposed to traumatic war experiences show higher rates of mental health disorders, particularly of PTSD, than those with low or no exposure or nondeployed veterans (IOM, 2008b). The *Gulf War and Health, Volume 6* report on deployment-related stress (IOM, 2008b) found a dose–response relationship between the degree of traumatic war exposure and PTSD, but deployment to a war zone even without direct combat exposure could be considered to be a risk factor for the development of PTSD and other mental health disorders such as anxiety and depressive disorders (Ikin et al., 2004). Recent studies of Gulf War veterans continue to show that being in combat and exposed to dead, wounded, and dying people adversely affects mental health (Gade and Wenger, 2011); increases the likelihood of developing PTSD but not depression (Maguen et al., 2011); and leads to a higher level of postdeployment substance abuse, particularly alcohol use (Kelsall et al., 2015; Maguen et al., 2011). One large study that assessed Gulf War veterans over time, found that between 1995 and 2005, the number of deployed veterans with PTSD increased significantly ($p < 0.05$) from 12.01% to 14.4%, and this rate was three times that of nondeployed veterans (3.9% and 4.0%, respectively) (Li et al., 2011a).

Other studies have found that the presence of PTSD increases the risk of having other psychiatric and physical conditions (IOM, 2012).

Conclusions

A well-accepted reality in today's medical practice is the frequent co-occurrence of chronic physical conditions such as diabetes, hypertension, and cancer with mental health conditions such as depression, anxiety, and PTSD. This co-occurrence of health conditions can make it difficult to disentangle the physical from the psychological components of these conditions.

The Volume 10 committee identified only one new primary study and two secondary studies that provided new information on the mental health status of Gulf War veterans. The primary study found that even 20 years after the war, deployed Australian veterans continued to have a greater prevalence of PTSD and were more likely to develop PTSD than nondeployed veterans. Two secondary studies also supported the finding that even many years after the war, U.S. and Danish Gulf War veterans experience more PTSD, depression, and other mental health conditions than nondeployed veterans.

The committee finds that associations between Gulf War service and PTSD, generalized anxiety disorder, substance abuse, and depressive disorders are well established. Furthermore, the committee finds that monitoring and treating these issues and the mental and physical problems that may have caused them deserves greater attention than additional studies that seek to examine their relationship to Gulf War deployment.

The committee recognizes that comparing combat-related PTSD in deployed and nondeployed veterans is not necessarily the best approach for determining the risk of PTSD in

either group. Nondeployed veterans cannot have PTSD related to non-existent combat experiences. However, as noted in the Summary of Volumes 4 and 8 section, some of the studies reviewed in the earlier volumes reported that increased levels of combat exposure may result in an increase in PTSD among the deployed veterans, that is, the greater the exposure the more likely the development of PTSD and the more severe its symptoms. Interestingly, even years after the war, deployed veterans continue to show a greater prevalence of PTSD (combat related or otherwise was not specified) and a greater risk for new incidence of it than nondeployed veterans (Sim et al. 2015). Whether the cause of the PTSD in later years is deployment or a post-war exposure was not stated in the study of Australian veterans. As noted in the IOM reports on PTSD (IOM, 2012, 2014), although delayed onset PTSD can occur, it is not common. Furthermore, some veterans may have many of the symptoms of PTSD for years, but initially may not have met the full criteria for such a diagnosis. Future long-term studies of PTSD in Gulf War veterans or other veteran groups would be enhanced by providing information on the traumatic event that precipitated the development of PTSD in both deployed and nondeployed veterans. For the most part, the studies reviewed by Gulf War and Health committees, including this committee, have not adequately determined the cause of PTSD in any of the veterans. The use of screening measures, without subsequent diagnostic assessments, is inadequate to make this determination.

Therefore, the Volume 10 committee concludes that there is sufficient evidence of a causal relationship between traumatic experiences during deployment to the Gulf War and PTSD. The committee also concludes that there is sufficient evidence of an association between deployment to the Gulf War and generalized anxiety disorder, depression, and substance abuse (particularly alcohol abuse).

TABLE 4-9 Mental and Behavioral Health Conditions

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Volumes 4 and 8 Primary Studies						
Black et al., 2004b (Vol. 4)	Population-based interview study, by telephone; stratified random sample with proportional allocation (cohort from Iowa Persian Gulf Study Group, 1997)	1,896 GWVs vs 1,799 NDVs listing Iowa as home state at time of enlistment	PRIME-MD (MDD, panic disorder, GAD) PCL-M, combat exposure assessed in basic demographic questionnaire CAGE questionnaire (alcohol abuse)	Panic disorder (OR = 2.2, 95% CI 1.2–3.8); GAD (OR = 2.5, 95% CI 1.5–4.1); PTSD (OR = 2.5, 95% CI 1.2–5.0); any anxiety disorder (OR = 2.3, 95% CI 1.5–3.5)	Age, sex, race, branch of military, rank, military status, prior mental health condition	Large, population-based sample
Barrett et al., 2002 (Vol. 4)	Population-based survey; completed telephone survey about their health status (same population as Black et al., 2004b)	3,682 GWVs and control subjects	PCL-M, SF-36	Persons screened positive for PTSD more likely to have been deployed to Gulf War (OR = 2.02, 95% CI 0.97–4.23) PTSD associated with: current smoking status (OR = 3.83, 95% CI 1.40–10.46); number of self-reported symptoms (19.83 symptoms with PTSD vs 3.64 with no PTSD, $p < 0.0001$); number of medical conditions (1.73 conditions with PTSD vs 10.18 with no PTSD) Lower SF-36 scores for physical functioning (93 vs 66, $p < 0.0001$) and general health (80 vs 33, $p < 0.0001$)	Deployment status, age, sex, race, rank, branch, military status, and smoking status	Brief PTSD screen used; used 50 as the cutoff score with the PCL-M; low number of subjects who screened positive for PTSD; the sample from Iowa might not be representative of all U.S. military personnel
Black et al., 2004a	Nested case-comparison;	602 veterans and controls	SCID (face-to-face interviews); SNAP;	PTSD (27% vs 5% in deployed vs controls, OR = 7.1, 95% CI	Validated PTSD checklist against	

Study	Design	Population	Outcomes	Results	Adjustments	Comments
(Vol. 4)	face-to-face interviews		SF-36; Whitely Index	2.1–24.2); anxiety disorders (52% vs 25%, OR = 3.2, 95% CI 1.6–6.3); any disorder (68% vs 52%, OR = 2.0, 95% CI 1.0–3.7)	SCID (70.4% sensitivity and 86.2% specificity of questionnaire for the 192/602 subjects who met the criteria for depression)	
Kang et al., 2003 (Vol. 4)	Cross-sectional; population-based stratified random sample of GWV deployed compared with those deployed elsewhere	11,441 deployed vs 9,476 deployed elsewhere	Mail survey and telephone-based survey of PTSD symptoms	GWV (12.1%) compared to deployed elsewhere veterans (4.3%); OR = 3.1 (95% CI 2.7–3.4)	Sex, age, marital status, rank, and unit component	Nationally representative sample, questionnaire only
Wolfe et al., 1999a,b; Proctor et al., 1998 (Vol. 4)	Cross-sectional survey and interviews from larger cohorts followed longitudinally	220 Ft. Devens vs 73 New Orleans vs 48 Germany; New Orleans and Germany cohorts only studied at time 2	Health Symptom Checklist, Mississippi PTSD Scale (times 1[day of arrival home] and time 2 [2 yrs later]), SCID, CAPS (clinician diagnostic interviews, time 2 only)	Risk factors for PTSD were being female (time 1 OR = 3.2, 95% CI 1.9–5.5; time 2 OR = 2.3, 95% CI 1.5–3.5) and having high combat exposure (time 1 OR = 1.22, time 2 OR = 1.12, $p < 0.05$ for both); PTSD also highly correlated with current major depression (r = 0.35, $p < 0.001$) Lifetime occurrence of PTSD more prevalent in Ft. Devens (8.1%) and New Orleans (7.6%) vs Germany (0%), no p value reported Prevalence of PTSD increased from time 1 (3%) to time 2 (8%) in Ft. Devens group, 2% of the study group had PTSD at both	Sex, reported health symptoms	Small sample deployed to Germany, 78% participation rate; Wolfe, 1999b, used direct interviews

Study	Design	Population	Outcomes	Results	Adjustments	Comments
				time 1 and time 2, 1% had PTSD at time 1 but not time 2, and 6% had PTSD at time 2 but not time 1		
Brailey et al., 1998 (Vol. 4)	Longitudinal; psychological interviews 9 months after war, and subgroup follow-up at 16 months; Louisiana National Guard and Reserve troops	876 deployed (349 at time 2, 16 months later) vs 396 nondeployed	BDI-II, State Anger; State Anxiety; BSI Depression; BSI Anxiety; BSI Hostility, the HSC, PCL, and the Mississippi Scale	Prevalence of depression increased over time in deployed veterans from time 1 (6.9%) to time 2 (13.8%), as did prevalence of PTSD (2.3% to 10.6%) and hostility (4.9% to 13.8%); no *p* values reported	Age, education	Large attrition by time 2 (39.8% response rate at follow-up)
Ikin et al., 2004 (Vol. 4)	Cross-sectional survey of all Australian deployed veterans	1,381 GWVs vs 1,377 comparison veterans	CIDI	Prevalence of any disorder: 31% in GWVs vs 21% in comparison group; PTSD: OR = 3.9 (95% CI 2.3–6.5); MDD: OR = 1.6 (95% CI 1.3–2.0); alcohol abuse: OR = 1.5 (95% CI 1.2–2.0)	Service type, rank, age, education, marital status	GWVs younger, more likely in the Navy, and lower ranked than comparison group Large sample, well-validated psychological interview tool; low participation bias
Dlugosz et al., 1999 (Vol. 4)	Post-war hospitalizations June 1991–September 1993	Active-duty men (1,775,236) and women (209,760) June 1991–September 1993; GWVs vs NDV	ICD-9 CM categories for 10 mental health disorders	GWVs had increased risk of hospitalizations due to: acute reactions to stress (RR = 1.45, 95% CI 1.08–1.94); drug-related disorders (RR = 1.29, 95% CI 1.10–1.52) No general increase in alcohol-related diagnoses, but serving in ground war in Iraq associated with alcohol-related	Age, sex, service-branch adjusted rates	Active duty only; no assessment of outpatient treatment

Study	Design	Population	Outcomes	Results Adjustments	Comments
				hospitalizations in men (RR = 1.13, 95% CI 1.04–1.23)	
Ismail et al., 2002 (Vol. 8)	Two-phase cohort study	Random sample of UK GWVs with reported disability (n = 111) and no disability (n = 98) and era and Bosnia veterans with disability (n = 54) and no disability (n = 79); Disability defined as score < 72.2 on SF-36	DSM-IV disorders assessed during clinician-administered interview	Disabled GWVs compared to disabled controls: No increase in prevalence of any mental health disorder except undifferentiated somatoform disorder (OR = 3.1, 95% CI 1.0–9.6)	Response rate good in GWV (67% disabled and 62% nondisabled), but low in controls (55% and 43%) Strength: clinician-administered interview
Fiedler et al., 2006 (Vol. 8)	Cross-sectional, random sampling of all U.S. GWVs vs NDVs; assessment by computer-assisted telephone interview	967 GWVs vs 784 NDVs	CIDI	Deployed veterans had significantly higher 12-month prevalence of any psychiatric disorder compared to nondeployed, (26.1% vs. 16.1%, $p < 0.05$) Increase in MDD (14.2% vs 7.2% for males and 25.3% vs 11.8% for females) and PTSD (3.4% vs 0.7% for males and 4.0% vs 2.2% for females), no p value reported All deployed vs all controls: Any anxiety disorder (OR = 1.81, 95% CI 1.34–2.45);	Response rate 59% for GWV, 51% for NDVs Female gender, divorced, and lower rank were significant independent risk factors

Study	Design	Population	Outcomes	Results	Adjustments	Comments
				depression (OR = 2.07, 95% CI 1.50–2.85) Males: alcohol dependence (4.8% vs 3.3%, NS); drug dependence (1.2% vs 0.0% $p <$ 0.05)		
Toomey et al., 2007 (Vol. 8)	Cross-sectional survey; stratified random sample of U.S. deployed vs nondeployed veterans; structured interview, self-report of symptoms	1,061 GWVs vs 1,128 NDVs (same cohort as Eisen et al., 2005)	CAPS; CIDI; PTSD Checklist; BDI-II; BAI; SF-36; QoLI; CES	Gulf War era onset: PTSD (6.2% GWVs vs 1.1%, NDVs), (OR = 5.78, 95% CI 2.6–12.7); non-PTSD anxiety disorders (4.3% GWVs vs 1.4% NDVs), (OR = 3.79, 95% CI 1.8–8.0); MDD (7.1% GWVs vs 4.1% NDVs), (OR = 1.81, 95% CI 1.0–3.2) 10 years post-Gulf War era: PTSD (1.8% vs 0.06% GWVs vs NDVs, p = 0.12); non-PTSD anxiety disorders (2.8% vs 1.2% GWVs vs NDVs, p = 0.01); major depression (3.2% GWVs vs 0.8% NDVs, p = 0.01) Symptom self report: GWVs reported more severe symptoms of PTSD, depression, anxiety; lower-level quality of life; SF-36 scores significantly lower	Age, sex, ethnicity, years of education, duty type (active vs reserve/guard), service branch, rank	Response rate: 53% for GWVs; 39% for NDVs Prevalence of non-PTSD anxiety disorders with onset prior to war was significantly higher in GWVs (12.5%) vs NDVs (9.2%), p = 0.02
Al-Turkait and Ohaeri, 2008 (Vol. 8)	Retrospective cohort; stratified random sampling of four groups of veterans: retired from military prior to war; active duty with	200 Kuwaiti Gulf War veterans, 50 from each group	PTSD, determined by CAPS	POWs: 48.4% Combat: 32% No combat: 22% Retired: 24% Higher rates of anxiety, depression, and low self-esteem in those with PTSD compared to those without PTSD (p =		Potential bias resulting from application of questionnaire to a foreign population

Study	Design	Population	Outcomes	Results	Adjustments	Comments
	no combat; active duty with combat; POW			0.0001)		
Volume 10 Primary Study						
Sim et al., 2015	Cohort study Longitudinal health survey conducted in 2011–2012 as follow-up to baseline 2000–2002 Australian Gulf War Veterans' Health Study;	All 1,456 male Australian Gulf War veterans and 1,588 NDVs in comparison group; 715 GWVs and 675 NDVs participated in follow-up study	Mental health status based on SF12 and GHQ-12 CIDI via phone interview used to measure 12-month PTSD, alcohol disorder, MDD, specific phobia, social phobia, bipolar disorder, and obsessive compulsive disorder Included Australian Department of Veterans Affairs health data and data from Medicare, Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme claims PTSD also based on self-reported	GWVs had significantly worse physical (adj mean diff = -1.34) and mental health (-3.32) than NDVs. Both groups reported sig worse physical and mental health from baseline to follow-up No significant difference in groups reporting depression, but GWVs were more likely to have mild or moderate symptoms No significant changes from baseline to follow-up GWVs (approx. 7.3–8.2% vs 2.7–4.8%) reported significantly more PTSD by all 3 methods (RRs = 1.56 to 2.94) than NDVs, and greater prevalence from baseline to follow-up (RR = 1.96, 95% CI 1.29–2.97) but not in NDVs Significantly more GWVs had current alcohol use disorder per CIDI and AUDIT (RRs = 1.93 and 1.26) Significantly higher prevalence in GWVs from baseline to	Age, rank category, and service branch	Participation rate: 54% in GWVs and 47% in NDVs First survey conducted in 2003 Derivative of Kelsall et al., 2009

Study	Design	Population	Outcomes	Results	Adjustments	Comments
			symptoms and PCL, and report of doctor-diagnosed PTSD in the past 12 months Alcohol and substance use disorders based on self-reports using CIDI, AUDIT, and doctor-diagnosed disorders in the past 12 months.	follow-up (RR = 2.0, 95% CI 1.25–3.2) but not in NDVs (RR = 1.78, 95% CI 0.84–3.76)		

NOTE: AUDIT = Alcohol Use Disorders Identification Test; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory; BSI = Brief Symptom Inventory; CAPS = Clinician Administered PTSD Scale; CES = Combat Exposure Scale; CI = confidence interval; CIDI = Composite International Diagnostic Interview; DSM-IV = Diagnostic and Statistical Manual of Mental Health Disorders, fourth edition; GAD = generalized anxiety disorder; GHQ-12 = 12-Item General Health Questionnaire; GWV = Gulf War veteran; HSC = Health Symptoms Checklist; ICD = International Classification of Diseases; MDD = major depressive disorder; NDV = nondeployed veteran; NS = not significant; OR = odds ratio; PCL = PTSD Checklist; PCL-M = PTSD Checklist–Military Version; POW = prisoner of war; PRIME-MD = Primary Care Evaluation of Mental Disorders; PTSD = posttraumatic stress disorder; QoLI = Quality of Life Inventory; RR = risk ratio; SCID = Structured Clinical Interview for DSM Disorders; SNAP = Special Needs Assessment Profile; SF-12 = 12-Item Short Form Health Survey; SF-36 = 36-Item Short Form Health Survey; UK = United Kingdom; U.S. = United States.

NEUROLOGIC CONDITIONS

Neurologic conditions have been associated with a variety of environmental exposures, such as those experienced by Gulf War veterans while deployed. In addition to exposures to nerve agents, organophosphate pesticides, and prophylactic agents such as pyridostigmine bromide, exposure to combat with its inherent and immediate risk of traumatic brain injury (TBI) and traumatic peripheral nerve injury can also result in the subsequent development of posttraumatic neurologic conditions including localization-related epilepsy and cognitive disorders related to focal and diffuse TBI. Other risk factors for the development of specific neurologic disorders include age and family history. Among the neurologic problems that have been studied following deployment to the Gulf War are peripheral nerve pain, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), immune-mediated neuropathies (including Guillain Barré syndrome), and migraines. In this section, the committee considers previous *Gulf War and Health* reports and new literature on neurologic conditions, specifically peripheral neuropathy, MS, ALS, and other neurodegenerative conditions in Gulf War veterans. In each section, the committee summarizes the findings and conclusions from *Gulf War and Health Volumes 4* and *8*, reviews the new literature published since Volume 8, and discusses any other studies that do not meet the criteria of a primary or secondary study but that nonetheless provide further information to assess neurological conditions in Gulf War veterans. All primary studies of neurologic conditions are summarized in Table 4-11 at the end of this section.

Peripheral Neurologic Disorders

Peripheral neuropathy may be defined as weakness, numbness, and pain in the nerves, typically, but not exclusively, in the hands and feet. Peripheral neuropathy can result from traumatic injuries, diabetes, alcohol abuse, infections, metabolic problems, inherited factors, and exposure to toxicants, including chemotherapeutic agents. This section reviews studies of peripheral mononeuropathy, polyneuropathy, or neuromuscular symptoms, as identified by the investigators conducting the studies.

Types of peripheral neurologic conditions and their diagnoses were characterized in Volumes 4 and 8 of the *Gulf War and Health* series and are not repeated here. This committee agreed with prior Gulf War and Health committees in that neurophysiologic studies with objective measures are especially helpful in determining the presence of neuropathy and are used in conjunction with clinical evaluations including diminished or absent distal deep tendon reflexes, distal or symmetric leg and foot weakness and atrophy, and change in sensation in toes and feet. Studies that include objective and quantitative measures, such as nerve conduction tests or more sophisticated neurophysiological tests, and even nerve biopsies, are optimal and considered to be primary studies. Studies that relied solely on self-reports of neuropathic symptoms (including numbness, neuropathic pain, weakness, among other related symptoms) were considered to be secondary.

Summary of Volumes 4 and 8

In Volume 4, two primary studies were identified. One was a large, well-designed population-based study of a VA cohort that looked at the presence of distal symmetric polyneuropathy in 1,047 deployed and 1,121 nondeployed Gulf War veterans. The neuropathy

was evaluated based on history, physical examination, and standardized electrophysiological assessment of motor and sensory nerves. Spouses of each group of veterans and 240 Khamisiyah-exposed veterans were also studied. That committee found that the distal symmetric polyneuropathy identified by nerve conduction was the best, most reliable measure of peripheral neuropathy. There were no significant differences between the deployed and nondeployed veterans in term of distal symmetric neuropathy, nor were there differences upon physical examination or self-reported peripheral neuropathy, although more deployed veterans reported numbness and tingling. The other primary study was a smaller evaluation of UK troops deployed to the Gulf War who handled pesticides and nerve agent prophylaxis. Objective neurologic and myopathic testing showed no significant differences between deployed and nondeployed veterans who had neuromuscular symptoms of Gulf War illness with the exception of greater effort on the bicycle exercise test.

The four secondary studies reviewed in Volume 4 also showed a lack of association between deployment and peripheral neuropathy on the basis of objective measures or were inconclusive. Some studies reported higher rates of peripheral neuropathy, but they used self-reports, which the committee did not accept as a reliable measure of peripheral neuropathy. The different case definitions of peripheral neuropathies used by researchers led to problems with ascertainment, and thus, it was difficult to make comparisons among studies.

The Volume 8 committee identified one additional primary study of Australian Gulf War veterans. On the basis of self-report, the deployed veterans had more lower-extremity symptoms that were considered to be possibly indicative of neuropathy but they did not differ from nondeployed veterans on the basis of neurologic examinations. The increased self-reports of neurological symptoms were associated with self-reports of immunizations and exposure to chemical agents including PB and pesticides. The authors found no clinical evidence of an increased risk of myopathy or muscle weakness across the entire cohort. *Therefore, the Volume 8 committee concluded that there was limited/suggestive evidence of no association between deployment to the Gulf War and peripheral neuropathy.*

New Literature

The Volume 10 committee did not identify any new primary studies that assessed the association between deployment to the Gulf War and peripheral neurologic disorders.

Secondary Studies

The committee found two studies that met its criteria for secondary studies because they were based on self-reports of health conditions. Sim et al. (2015) reported on the Australian Gulf War Veterans' FollowUp Health Study, conducted between 2011 and 2013. This study is an assessment of the entire 1,871 Australian Gulf War cohort 10 years after the 2000–2002 baseline study and 20 years after the war. Results were adjusted for age, rank category, and service branch. Of the 1,456 eligible deployed veterans, 715 participated in the study and 675 of the 1,449 nondeployed veterans provided the comparison group. Neuropathic symptoms were based on self-reports for 17 symptoms. Deployed veterans were significantly more likely to report at least one neuropathic symptom in the previous month than nondeployed veterans (60% vs 52%; RR = 1.13, 95% CI 1.03–1.25) and more likely to report at least four neuropathic symptoms (24% vs 18%; RR = 1.32, 95% CI 1.07–1.64). Among the symptoms of muscle weakness, the most significant differences were found for difficulty lifting object above head (RR = 1.42, 95% CI 1.13–1.79), difficulty getting up from sitting in a chair (RR = 1.25, 95% CI 1.06–1.48), and problems with tripping or feet slapping while walking (RR = 1.54, 95% CI 1.07–2.22); the

symptoms of sensory disturbance with the greatest differences were difficulty feeling pain, cuts, or injuries (RR = 3.25, 95% CI 1.45–7.30), and unusual sensitivity or tenderness of skin when clothes or bedclothes rub against the person (RR = 2.07 95% CI 1.23–3.46); the difference in the one symptom of autonomic dysfunction (feeling faint when standing up from lying or sitting) was not significant.

The wave 3 survey of the cross-sectional National Health Study of Persian Gulf War Era Veterans was conducted in 2012–2013 and asked 8,104 deployed and 6,148 Gulf War era veterans to indicate whether a doctor had ever told them they had a medical condition and then whether the condition had been present in the previous 4 weeks (Dursa et al., 2016). There was a significant difference in the self-reports of neuralgia between the deployed and era veterans (9.4% vs 6.3%; OR = 1.65, 95% CI 1.40–1.95). The OR was adjusted for age, race, sex, BMI, smoking status, service branch, and unit component.

Other Related Studies

VA provided a health care use report for Gulf War deployed and era veterans who sought care in VA facilities from October 2001 to December 2013. The report presented the prevalence of diagnoses of diseases by ICD-9 code categories, including diseases of the nervous system and sense organs (ICD-9 codes 320–389). 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. A total of 286,995 Gulf War deployed and 296,635 era veterans received treatment at VA over the approximately 11-year period (VA, 2014a,b). These VA health care users represent 46% of all deployed Gulf War veterans and 36% of all nondeployed era veterans. Of these veterans, 166,396 (58.0%) deployed veterans and 156,772 (58.1%) nondeployed veterans had any diagnosis for ICD-9 codes 320–389. Of these, 11.9% of deployed veterans and 11.8% of nondeployed veterans had a diagnosis of mononeuritis of the upper limb or mononeuritis multiplex (VA, 2014a,b).

Conclusions

The primary studies that assessed peripheral neuropathy used objective measures, clinical examinations, or both to diagnose the damage. These studies uniformly found no association between deployment to the Gulf War and peripheral neuropathy in the veterans. However, several of the secondary studies that relied on self-reports of neurological problems did find increased reporting of those problems among veterans who had deployed to the Gulf War when compared with nondeployed veterans. The committee believes that objective measures are a more reliable diagnostic tool than self-reports.

It is reasonable to consider polyneuropathy to have two phases of expression. The first is related to proximate exposure in the field due to some hypothesized toxic factor (e.g., pesticide exposure), and the second is late in life with deployment to the Gulf War serving as a modifying factor. That is, perhaps some exposure experienced during the Gulf War would make a veteran more likely to express polyneuropathy in later life, whether as an idiopathic entity or even in a veteran with a known causal factor, such as a nutritional or diabetic neuropathy, or even Charcot-Marie-Tooth disease (one of the most common genetic neurologic conditions). Although the committee recognizes that these phases are speculative, they do argue for peripheral neuropathy as a continuing area of study in aging Gulf War veterans; however, the committee also emphasizes that age itself is one of the stronger factors associated with symmetric loss of ankle jerk reflexes, which is often asymptomatic, but is nonetheless an objective evidence of polyneuropathy.

Therefore, the Volume 10 committee concludes that there is limited/suggestive evidence of no association between deployment to the Gulf War and objective measures of peripheral neurologic conditions.

Multiple Sclerosis and Related Neuroinflammatory Conditions

MS is a chronic inflammatory disease of the brain and spinal cord caused by an immune-mediated attack primarily on the myelin membrane that surrounds and insulates nerve fibers (axons) that are responsible for normal transmission of electrical and chemical information in the nervous system. MS can vary from a relatively benign illness to a rapidly evolving and incapacitating disease. Symptoms of MS—such as weakness of the limbs, numbness, visual loss or blurring, pain, imbalance, fatigue, slowed thinking, and bladder/bowel/sexual dysfunction—reflect the loss of neural connections required for normal function.

MS affects about 400,000 people in the United States and is approximately three times more common in women than men (Multiple Sclerosis Association of America, 2015). The age of onset is typically between 18 and 40 years of age, but the disease can present across the life span. MS also appears to be increasing in frequency in multiple populations, especially in women. The environmental factors that influence MS are not known; however, several risk factors have been implicated in the development of MS including infection with Epstein-Barr virus, ultraviolet light exposure and vitamin D status, and cigarette smoking (Wingerchuk, 2011).

Summary of Volumes 4 and 8

No literature on MS was available for review in Volume 4, but one secondary study was reviewed in Volume 8 (a primary study on mortality from MS is discussed in the section "Causes of Mortality"). The small secondary study (Kelsall et al., 2005) did not show any increased risk for MS in the deployed Australian Gulf War cohort. *Therefore, the Volume 8 committee concluded that there was inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and MS. The Volume 8 committee recommended that additional well-designed, adequately powered studies of MS incidence following deployment are needed.*

New Literature

Primary Study

The committee identified one new primary study that assessed the association between deployment to the Gulf War and MS. Wallin et al. (2014) assembled an incident cohort of veterans of the Gulf War who had been on active-duty military service during the 1990–1991 war. Cases of MS were identified based on VA Compensation and Pension files for service connection for MS for 17 years after the war. Service connection for MS requires definitive evidence of clinical signs of MS upon examination during or within 7 years after military service. The authors found 330 cases of MS among the 696,118 deployed veterans (250 in males and 80 in females) and 1,230 cases among the 1,780,215 nondeployed veterans (837 in males and 393 in females), resulting in a total relative risk of 0.69 (95% CI 0.61–0.78) for MS in deployed versus nondeployed. The RR for men was 0.72 (95% CI 0.62–0.83) and 0.96 for women (95% CI 0.75–1.22).

Wallin et al. (2014) also assessed the association between deployment to the Gulf War and neuromyelitis optica and other neurologic conditions that the authors grouped under the term

"other demyelinating disease" (ODD), that is demyelinating conditions other than MS. ODD also included possible MS (compared with definite MS), transverse myelitis, optic neuritis, and other clinically isolated syndromes. An incident cohort of 57 deployed veterans of the Gulf War who had an ODD diagnosis was compared with 224 nondeployed ODD-diagnosed veterans of the same era. Possible MS was the most common ODD, followed by optic neuritis. The absolute risk (17-year cumulative risk) for any ODD was 8.19 for deployed personnel (57 cases in 696,118 service members) and 12.54 for nondeployed personnel (224 cases in 1,786,215 service members). Further analysis comparing deployed with nondeployed veterans was not conducted.

Secondary Studies

The committee found two studies that met its criteria for secondary studies. In the Sim et al. (2015) Australian Gulf War Veterans' Follow Up Health Study discussed in the previous section on peripheral neurologic disorders, only 1 of the 697 deployed male Australian Gulf War veterans and 1 of the 659 nondeployed veterans reported a doctor-diagnosed case of MS.

Dursa et al. (2016) reported results from the third wave of the cross-sectional National Health Study of Persian Gulf War Era Veterans that was conducted in 2012–2013 and asked 8,104 deployed and 6,148 Gulf War era veterans whether a doctor ever told the veteran that they had multiple sclerosis. The adjusted OR for self-reported MS in the deployed versus nondeployed veterans was 1.35 (95% CI 0.72–2.51) and the prevalence was 0.6% and 0.5%, respectively.

Conclusions

Together the new primary study and the two additional secondary studies, combined with the study in Volume 8, indicate that Gulf War veterans do not have an increased risk of developing MS.

Therefore, the Volume 10 committee concludes that there is limited/suggestive evidence of no association between deployment to the Gulf War and multiple sclerosis.

Amyotrophic Lateral Sclerosis

ALS, often referred to as Lou Gehrig's disease, motor neuron disease, or Charcot's disease, is a neuromuscular disease that affects approximately 20,000 to 30,000 people in the United States (ALS Association, 2008; National Institute of Neurological Disorders and Stroke, 2006, 2009). ALS affects all races and ethnic backgrounds, and the risk is higher in men than women of the same age (Annegers et al., 1991). The disease is almost always fatal, although the rate of progression varies from patient to patient.

ALS causes degeneration of the motor neurons in the cerebral motor cortex, the brain stem, and the spinal cord (Rowland, 2000). The motor neurons are nerve cells that provide communication between the highest levels of the nervous system and the voluntary muscles of the body (National Institute of Neurological Disorders and Stroke, 2006). When the upper motor neurons degenerate, their connections to the lower motor neurons and spinal interneurons are disrupted, leading to muscle weakness and spasticity. Lower motor neuron degeneration disrupts nerve contact to the muscles resulting in muscle atrophy. Eventually, affected people are unable to move their arms and legs and cannot speak or swallow. When the connection between the neurons and the muscles responsible for breathing is disrupted, patients either die from

respiratory failure or require mechanical ventilation to continue to breathe. The majority of persons with ALS die from respiratory failure within 5 years from the onset of symptoms. To be diagnosed with ALS, patients must have signs and symptoms of both upper and lower motor neuron damage that cannot be attributed to other causes.

While most cases of ALS are sporadic, about 10% of cases are transmitted through families as a dominant trait (Sreedharan and Brown, 2013). These inherited forms of ALS have provided a powerful opportunity to dissect pathological events that trigger motor neuron disease. The gene most commonly mutated in ALS (about 40–45% of familial cases and 5–8% of sporadic cases in the United States) is also implicated in frontotemporal dementia; it is designated C9orf72 (Dejesus-Hernandez et al., 2011; Gijselnck et al., 2012; Renton et al., 2011). Some variability in C9orf72 prevalence by race/ethnicity and country of origin exists in both sporadic and familial ALS (Majounie et al., 2012).The defect is expansion of intronic hexanucleotide repeats. The second most common ALS gene is superoxide dismutase, whose mutations (usually missense changes) account for approximately 20% of ALS cases. Mutations in the RNA binding proteins FUS/TLS and TDP43 each account for approximately 5% of cases. All told, there are upwards of 50 ALS genes with clear Mendelian inheritance and more than 120 that may bear on the genetic risk of ALS.

Several hypotheses purport to explain why these mutations are pathogenic (Ling et al., 2013; Peters et al., 2015). Many mutations, like SOD1, lead to protein instability and aggregation with multiple adverse effects on cellular metabolism. Others, like FUS/TLS (Kwiatkowski et al., 2009) and TDP43 (Sreedharan et al., 2008), perturb RNA metabolism both within the cell body and in dendrites and axons. Toxicity of the C9orf72 expansions probably arises in part from deposition of RNA foci in cell nuclei, which sequesters intranuclear proteins, disturbances of nuclear membrane transport, and in part via expression of toxic dipeptides through atypical protein translation.

The causes of sporadic ALS are not well defined, but may include complex interactions of multiple gene variants, exposure to environmental toxins, and activation of endogenous retroviruses, as well as occupational, socioeconomic, demographic, and life style risk factors (Li et al., 2015; Mayo Clinic, 2014). Despite a number of epidemiologic studies examining environmental, occupational, socioeconomic, demographic, and life style risk factors for ALS, to date no consistently identified nongenetic risk factors have been reported (Armon, 2003, 2004; Armon et al., 1991; Cermelli et al., 2003; Chio et al., 2005; Kamel et al., 2002; McGuire et al., 1996, 1997; Nicolson et al., 2002; Rowland, 2000; Valenti et al., 2005).

Summary of Volumes 4 and 8

In Volume 4, two primary studies (Coffman et al., 2005; Horner et al., 2003) and one secondary study (Haley, 2003) found that deployed veterans appear to be at increased risk for ALS. In the nationwide epidemiologic case ascertainment study, Horner et al. (2003) found an almost two-fold increase in the risk of ALS for the deployed Gulf War veterans compared with nondeployed (RR = 1.92, 95% CI 1.29–2.84). In a further study of the same data using capture–recapture analysis, Coffman et al. (2005) confirmed the nearly doubled risk. A secondary study found a slightly higher relative risk but within the same overall range when Gulf War veterans were compared to the general U.S. population. Other U.S. and UK mortality studies and a hospitalization study have not found an excess risk of ALS in Gulf War veterans (see the section on causes of mortality in this chapter). The Volume 4 committee concluded that further follow-up was warranted.

In Volume 8, one new primary study (Horner et al., 2008) extended the follow-up of the author's earlier study through 2001 and described a short-term increase in ALS risk in the deployed Gulf War veterans during the decade after the war. These analyses together support an estimate of a near doubling in risk among deployed veterans compared with nondeployed veterans. *The Volume 8 committee concluded that there was limited/suggestive evidence of an association between deployment to the Gulf War and ALS; however, further follow-up was warranted.*

New Literature

Primary Study

The committee identified one new primary study of ALS in Gulf War veterans by Kasarskis et al. (2009). This extension of the earlier epidemiologic studies by Horner et al. (2003, 2008) included an additional 28 veterans identified during the 2001–2002 follow-up surveillance period for a total of 43 deployed and 66 nondeployed veterans with ALS (deployment status was based on designation by the Defense Manpower Data Center [DMDC]). Median ventilator-free survival time for deployed veterans was significantly less than that of nondeployed veterans (40.2 vs 57.0 months, HR = 0.62, 95% CI 0.40–0.96, $p = 0.03$) when adjusted for age and neuroanatomical region of onset of clinical disease.

Secondary Studies

Only two studies met the committee's criteria for a secondary study. In the Australian Gulf War Veterans' Follow Up Health Study discussed in the previous sections, Sim et al. (2015) found that only 2 of the 697 deployed male Australian Gulf War veterans had ALS and none of the 659 nondeployed veterans reported having ALS. Given the few cases of ALS, statistical analyses could not be conducted.

The committee also considered the results from Dursa et al. (2016) on the third wave of the National Health Study of Persian Gulf War Era Veterans (discussed in the previous section). The adjusted OR for self-reported ALS in the deployed (0.1% of 8,104) versus era (0.05% of 6,148) veterans was 4.32 (95% CI 0.82–21.74; adjusted for age, race, sex, BMI, smoking status, service branch, and unit component).

Other Related Studies

Miranda et al. (2008) attempted to link the risk of developing ALS in deployed military personnel to specific geographic areas in the Gulf War region using geographic information system modeling. They found that the estimated ALS risk was greatest, although not statistically significant, for troop units with a potential exposure to nerve agents resulting from the munitions destruction at Khamisiyah (RR = 1.7, 95% credible interval[11] 0.7–3.7). The authors cautioned, however, that there may have been other unknown exposures in the plume that may account for the increased risk.

Conclusions

The one new primary study and the two new secondary studies provided further information on the association between ALS and deployment to the Gulf War. Only one of the studies indicated an increase in ALS among the deployed veterans compared with nondeployed veterans. One study suggested that deployed veterans had a more rapid decline than nondeployed

[11] "Essentially a Bayesian version of a confidence interval" (Miranda et al., 2008).

veterans although no explanation for this outcome was suggested. Thus, the new literature does not substantially alter the Volume 8 conclusion, including the need for further follow-up of veterans with and without ALS and both deployed and nondeployed. Since the publication of Volume 8, a substantial growth of knowledge has occurred regarding genetic risk alleles as well as highly penetrant genes associated with ALS. The absence of this information in prior studies is an important limitation in fully understanding the scope of risk of ALS and Gulf War deployment.

Therefore, the Volume 10 committee concludes that there is limited/suggestive evidence of an association between deployment to the Gulf War and amyotrophic lateral sclerosis; however, further follow-up continues to be warranted.

Other Neurodegenerative Conditions

Alzheimer's disease is the most common neurodegenerative disorder and a cause of dementia in elderly populations. Parkinson's disease—primarily considered a movement disorder—is the second most common neurodegenerative disorder. Both have progressive courses and no known cure. The neurodegeneration in Parkinson's disease has been associated with a combination of repeated, prolonged, or chronic exposures to toxicants (particularly pesticides), genetic factors, gene–toxicants interactions, and aging-related effects. In contrast with the Parkinson's disease literature, the associations, if any, between Alzheimer's disease and related disorders and environmental toxicants, or their interactions with age or genetic factors, are not as well established.

Summary of Volumes 4 and 8

The committee was unable to identify any studies of dementia or Alzheimer's disease in Gulf War veterans for Volumes 4 and 8, or for the current study. This committee did not identify any new literature on Parkinson's disease in Gulf War veterans. The Volume 8 committee noted that Parkinson's and Alzheimer's diseases generally present later in life (usually after age 60) and thus, it is unlikely that Gulf War veterans would manifest symptoms or signs of these neurodegenerative disorders until they reach at least the sixth decade of life. *Therefore, the Volume 8 committee concluded that there is insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and other neurodegenerative conditions.*

New Literature

The committee only identified one new study that met the criteria for a secondary study of other neurodegenerative conditions in Gulf War veterans. Dursa et al. (2016) reported results from the third wave of the cross-sectional National Health Study of Persian Gulf War Era Veterans that was conducted in 2012–2013 and asked 8,104 deployed and 6,148 Gulf War era veterans whether a doctor ever told the veteran that they had Parkinson's disease. The weighted prevalence was 0.5% in both deployed and era veterans and the OR was not statistically significant (OR = 1.15, 95% CI 0.59–2.24). However, the committee noted that given the long latency of Alzheimer's disease, Parkinson's disease, and related disorders, associations may not be evident without longitudinal prospective monitoring of an aging Gulf War veteran population.

Conclusions

This committee concurs with determination of the Volume 8 committee that a very long latency period for these health outcomes is a possibility, and that current studies have inadequate follow-up time to assess whether risk for these disorders is increased among Gulf War veterans. Given the lack of new information on the prevalence or incidence of neurodegenerative disease among Gulf War veterans, the Volume 10 committee had no evidence on which to modify the Volume 8 conclusions.

Therefore, the Volume 10 committee concludes that there is insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and other neurodegenerative conditions; further follow-up is warranted.

Neurocognitive and Neurobehavioral Outcomes

This section contains an overview and update on neurocognitive and neurobehavioral performance in Gulf War deployed veterans compared with nondeployed veterans.

Summary of Volumes 4 and 8

In Volume 4 and 8, the committees defined primary studies as those "studies that used neurobehavioral tests that had previously been used to detect adverse effects in population-based research on occupational groups." In Volume 4, two primary studies found significant differences in neurobehavioral performance—specifically the Purdue Pegboard Test, the California Verbal Learning Test, and the Wisconsin Card Sorting Test—when deployed Gulf War veterans were compared with nondeployed veterans or those deployed elsewhere. Only one of the three secondary studies found a difference in neurocognition between the two groups. The Volume 8 committee identified two additional secondary studies. One study (Proctor et al., 2006) did not compare deployed with nondeployed veterans but rather looked at neurocognition with respect to putative level of exposure to sarin during deployment. The second study of participants from the National Health Study of Gulf War Era Veterans and Their Families Study, assessed veterans 10 years after the war. Deployed veterans scored poorly compared with nondeployed veterans on two of eight factors (Toomey et al., 2009). The study authors and the committee found that the results did not suggest overall impaired neuropsychological functioning.

In conclusion, primary studies of Gulf War deployed versus nondeployed veterans failed to demonstrate differences in cognitive and motor measures as determined through neurobehavioral testing. *Therefore, the Volume 8 committee concluded that there was inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and neurocognitive and neurobehavioral performance.*

New Literature

Primary Study

The committee identified one new study that met its criteria for a primary study. The committee did not identify any new secondary studies of neurocognitive or neurobehavioral performance in Gulf War veterans.

In 1997, Ishoy et al. (2004) examined neurobehavioral symptoms in 686 Danish Gulf War veterans and 231 nondeployed military controls that were matched to the deployed veterans

on age, gender, and profession. Subjects performed the Coordination Ability Test System (CATSYS) tests including its extensions, the tremor test and the sway test. Physicians administered a questionnaire on cognitive and psychological symptoms the veteran had experienced in the prior 12 months. Results indicated that compared with nondeployed veterans, deployed veterans reported statistically significant increases ($p \leq 0.001$) in concentration or memory problems, repeated fits of headache, balance disturbances or fits of dizziness, abnormal fatigue (not caused by physical activity), and problems sleeping all night. However, the CATSYS tests showed that for 23 of the 26 tests results there were no significant differences between the two groups; for the three tests for which the difference was significant ($p = 0.05$: hand supination/pronation test standard deviation; reaction time test standard deviation; and mean sway velocity), the differences between the two groups were small.

Other Related Studies

Wallin et al. (2009) assessed neuropsychologic performance in a sample of 41 veterans from the National Health Survey of Gulf War Era Veterans conducted in 1995. Twenty-five of the participants met the CDC definition of Gulf War illness, and the 16 controls did not. There were no statistically significant differences between the two groups for composite scores on the traditional and computerized neuropsychologic testing battery, which included verbal abilities, vigilance, processing speed, reading level, memory and learning, problem solving and reasoning, motor coordination, speed, and strength, and effort on testing (all $p \geq 0.1$). The veterans with Gulf War illness, however, did have significantly more impairment on the Personality Assessment Inventory for somatic complaints, anxiety, anxiety-related disorders, depression, mania, paranoia, and borderline personality disorders (all $p < 0.01$) but not for schizophrenia, antisocial features, or alcohol or drug problems.

Chao et al. (2010) studied the cognitive effects of possible exposure to sarin and cyclosarin on 40 exposed and 40 unexposed Gulf War veterans who were participating in a study of Gulf War illness at the San Francisco Veterans Affairs Medical Center between 2002–2007. Fifty-four percent of the exposed veterans and 59% of the unexposed veterans met the Fukuda et al. (1998) definition for chronic multisymptom illness. Study participants underwent a neuropsychological test battery. Test results showed no significant differences between the exposed and unexposed groups on measures of general verbal intelligence, attention, executive function, manual dexterity, visuospatial abilities, or memory. When subjects who failed the Test of Memory Malingering were removed from the analysis, there were no statistical differences between the groups for neurobehavioral functioning.

In a cross-sectional, follow-up study of 64 exposed and 64 "matched" unexposed veterans who underwent neuropsychological and magnetic resonance imaging (MRI) assessment, Chao et al. (2011) found exposed veterans committed more errors of omission and had slower responses on the Continuous Performance Test than unexposed veterans, but these were reported without correction for multiple comparisons. Regression analysis found that exposure to the nerve agents predicted the number of continuous performance test omission errors ($p = 0.02$).

Conclusions

The one new primary study found only a very small association between deployment to the Gulf War and a few adverse neurobehavioral outcomes in Danish veterans. There were no new secondary studies. These results echo those of the Volume 8 committee.

Therefore, the Volume 10 committee concludes that there is inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and neurocognitive and neurobehavioral performance.

Migraines

This section contains an overview and update on migraines in Gulf War veterans compared with nondeployed veterans. Many studies have included headaches as part of self-reported symptom checklists or clustered them with other symptoms related to a specific condition, such as chronic fatigue syndrome and Gulf War illness. For both chronic fatigue syndrome and Gulf War illness, as well as in general, more headaches are reported among deployed versus nondeployed veterans (Doebbeling et al., 2000; Haley et al., 1997b; Ishoy et al., 1999b; Kang et al., 2000, 2009; Kelsall et al., 2004a; Pierce, 1997; Proctor et al., 1998; Stretch et al., 1995; Unwin et al., 1999). Fewer studies have focused on migraine among Gulf War deployed and era veterans or looked at sex differences in prevalence. The latter point is important as three out of four people with migraines are women.

Summary of Volumes 4 and 8

Volumes 4 and 8 did not include any studies of migraine, and headaches were only considered within the symptom complex of Gulf War illness and chronic fatigue syndrome. The Volume 8 report also included one study under a section on female veterans' health that assessed the health of 525 women who had been on active duty or in the reserve or National Guard during the Gulf War, of whom 160 served in the Persian Gulf region (Pierce, 1997). The women were asked about their physical and emotional health 2 years after the war (time 1) and 4 years after the war (time 2). At time 2, deployed women were more likely than nondeployed women to report headaches ($p = 0.001$), regardless of the length of their deployment. Reported health problems were not related to whether the woman was on active duty, in the reserves, or a member of the National Guard. The Volume 8 committee did not make any conclusions regarding an association between deployment to the Gulf War and migraines or headaches.

New Literature

The Volume 10 committee did not identify any new literature that met its criteria for a primary study, but two secondary studies and one other related study were identified for migraine and other headache disorders in Gulf War veterans.

Secondary Studies

The Australian Gulf War Veterans' Follow Up Health Study, conducted between 2011 and 2013, assessed the entire Australian Gulf War cohort 10 years after the 2000–2002 baseline study and 20 years after the war (Sim et al., 2015). This study was a follow-up to the Kelsall et al. (2004b), baseline study discussed in Volumes 4 and 8. Results were adjusted for age, rank category, and service branch, but not for smoking. Of the 1,456 eligible deployed veterans, 715 participated in the study and 675 of the 1,449 nondeployed veterans provided the comparison group; women were not included in the analysis. Health outcomes were based on self-reports and on self-reports of doctor-diagnosed conditions. Deployed veterans were slightly but not statistically significantly more likely to report doctor-diagnosed migraines (RR = 1.06, 95% CI 0.66–1.70). Using a 63-item symptom checklist, 60.2% of deployed veterans and 49.2% of era

veterans reported headaches in the last month. Deployed veterans were statistically significantly more likely to report headaches compared with era veterans (RR = 1.19, 95% CI 1.08–1.31). The change in the prevalence of headaches reported between deployed and era veterans was not statistically different. The incidence of headaches (not reported at baseline but reported 10 years later at follow-up)—43% of deployed and 29% of comparison veterans—was statistically significantly higher among deployed than era veterans (RR = 1.43, 95% CI 1.14–1.78).

The second study reviewed by the committee was results from the third wave of the National Health Study of Persian Gulf War Era Veterans, conducted in 2012–2013 (Dursa et al., 2016). The wave 3 survey asked 8,104 deployed and 6,148 Gulf War era veterans to indicate whether a doctor had ever told them they 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 of the survey were repeated. 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. Survey respondents were asked to indicate how much they had been bothered by headaches in the past 4 weeks. Questions elucidating potential confounders and risk factors such as experiencing head injury or TBI were not included. The weighted prevalence of migraine headache was 20.3% in the deployed and 16.1% in the era veterans. The odds of migraine headache were statistically significantly increased for self-reported migraine headache among the deployed compared with the era veterans (OR = 1.30, 95% CI 1.15–1.47; adjusted for age, race, sex, BMI, smoking status, service branch, and unit component). Weighted prevalence of headache was limited to study participants who self-reported having lifetime chronic multisymptom illness.

Other Related Studies

In the VA utilization reports discussed in the section on peripheral neuropathy earlier, 166,396 (58.0%) deployed veterans and 156,772 (58.1%) nondeployed veterans received any diagnosis for ICD-9 codes 320–389. Of these 20,473 (12.3%) deployed veterans and 17,599 (11.2%) nondeployed veterans had a diagnosis of migraine (VA, 2014a,b).

Conclusions

Migraines were not considered independently of symptom complexes of other conditions in Volumes 4 and 8. Two secondary studies were reviewed, but findings were not consistent. Among Australian veterans, the odds of migraine headache were statistically significantly increased for self-reported migraine for deployed compared with era veterans. Among U.S. veterans, deployed veterans did not report statistically significantly more doctor-diagnosed migraines compared with era veterans, but deployed veterans were statistically significantly more likely to report headaches compared with era veterans; over 13 years of follow-up, incident headaches were statistically significantly higher among deployed than comparison veterans.

Therefore, the Volume 10 committee concludes that there is inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and migraines and related headache conditions.

Other Neurologic Outcomes

Haley and colleagues performed detailed neurologic assessments in several case-control studies of Seabee reservists to investigate any possible neurologic underpinning of Gulf War illness. The cases were veterans who had met criteria for factor-derived syndromes defined by Haley et al. (see Chapter 3). Under the hypothesis that those veterans were ill from neurotoxic exposures, especially to organophosphates, the assessments covered broad neurologic function (Haley et al., 1997b), autonomic function (Haley et al., 2004), vestibular function (Roland et al., 2000), basal ganglia injury (Haley et al., 2000a,b), normalized regional cerebral blood flow (Haley et al., 2009); and paraoxonase (PON) genotype and serum concentrations (Haley et al., 1999). Separate groups of investigators also studied PON genotype or activity (Hotopf et al., 2003b; Mackness et al., 1997) and neuropsychologic functioning (Hom et al., 1997).

Summary of Volumes 4 and 8

The Volume 8 committee regarded the Seabee case-control studies as secondary studies primarily because of their lack of generalizability, strong potential for selection bias, and small sample sizes. Although their study design was characterized as nested case-control, the studies of Haley et al. are not true nested case-control studies. Cases were, appropriately, selected from the original cohort, but controls were not. With regard to the lack of generalizability, the authors selected as cases the most severely affected veterans—that is, those who scored highest on factor analysis-derived syndromes—whereas the Volume 8 committee thought that a random sample of those who met a particular case definition would be more appropriate.

The Volume 8 committee concluded that there is insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and other neurologic outcomes.

New Literature

The committee did not identify any new literature that met the criteria for a primary or a secondary study of other neurological outcomes in Gulf War veterans.

Conclusions

There was no new literature to supplement or contradict the conclusions of the Volume 8 committee.

Therefore, the Volume 10 committee concludes that there is insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and other neurologic outcomes.

Neuroimaging Studies of Gulf War Veterans

Overview of Studies

A number of studies using MRI of the brain have been published on veterans who have Gulf War illness. Veterans who participate in these studies usually have a diagnosis that meets the definition of Gulf War illness as established by Haley et al. (1997b) or by the CDC (Fukuda et al., 1998). These studies span the gamut of different MRI modalities—structural MRI, task activation functional MRI (fMRI), 1H MR spectroscopy (MRS), diffusion MRI, and perfusion MRI. Many of these studies attempt to identify correlations between imaging and clinical or

psychological findings, while others seek to identify a unique imaging biomarker for Gulf War illness. In this section, the committee considers the limitations of using MRI technology to identify, distinguish, and characterize neurologic conditions in veterans who have or do not have Gulf War illness.

The first limitation is that none of the MRI modalities themselves are specific for any disease or disorder. The small brain volume or reduced cortical thickness (i.e., atrophy) seen on structural MRI, response patterns on task fMRI, spectroscopic metabolite levels, spin diffusion metrics, and tissue perfusion of Gulf War veterans may also be seen in many other disease conditions (Fotuhi et al., 2012). For example, decreased brain volume—especially hippocampal atrophy—figures prominently in many structural MRI studies of Gulf War veterans. However, atrophy of various brain regions, particularly the hippocampus, is seen in many other conditions such as epilepsy; neurodegenerative disorders such as frontotemporal lobar degeneration syndromes and Alzheimer's disease; sleep disorders; developmental disorders; chronic stress; mental health disorders such as depression, anorexia and PTSD; head trauma; and ischemic cerebrovascular disease. Chao et al. (2014a) and Apfel et al. (2011) both found reduced hippocampal volume to be associated with PTSD in Gulf War veterans, but Chao (2014b) also found reduced brain volume to be associated with disturbed sleep efficiency in Gulf War veterans. Thus, brain atrophy, especially hippocampal atrophy, is not specific for, nor predictive of, Gulf War illness or Gulf War deployment, and any reported imaging findings are potentially attributable to other factors such as PTSD**.**

Other studies have analyzed N-acetyl aspartate (NAA), a brain metabolite visible on MRS, which reflects neuron number and health; it is often referenced as a ratio to creatinine (Cr). Decreased NAA/Cr levels in basal ganglia have been reported in veterans with Gulf War illness compared with veterans without Gulf War illness (Menon et al., 2004; Haley et al., 2000), but as with atrophy, decreased NAA/Cr is seen in a variety of other conditions and a direct relationship with Gulf War illness cannot be inferred.

Decreased NAA/Cr levels in basal ganglia have been reported in veterans who have Gulf War illness compared with veterans who do not have Gulf War illness (Menon et al., 2004; Haley et al., 2000b). In contrast, Weiner et al. (2011) found no evidence of reduced NAA/Cr in Gulf War veterans with Gulf War illness compared with veterans without Gulf War illness using both the CDC and Haley syndrome 2 definitions of Gulf War illness.

Task fMRI activation is a complex measure that reflects changes from the resting (control) state for both local blood flow and brain oxygen extraction in response to mental tasks. Differences in task activation patterns were found in various groups of veterans with Gulf War illness (Calley et al., 2010; Gopinath et al., 2012; Moffet et al., 2015; Rayhan et al., 2013d; Tillman et al., 2010), but altered task fMRI activation properties have been reported in many neurodegenerative, developmental, psychiatric, and other conditions.

Diffusion MRI is a measure of the magnitude and directionality of the diffusion of water in tissue. Intact tissue microstructure (e.g., white matter tracts, cell membranes, cell processes) impedes the random motion (diffusion) of water to a greater extent than tissue with disrupted microstructure. Diffusion MRI uses two common measures, mean diffusivity (MD) and fractional anisotropy (FA), to determine the integrity of tissue microstructure. MD is a scalar quantity, and the lower the MD value the more intact the tissue microstructure. FA is a vector quantity and the greater the FA value the more intact is the white matter tract myelination. The component measures that contribute to FA (radial versus axial diffusivity) are sometimes analyzed separately; however, detailed modeling studies have called into question the validity of

this approach (Wheeler-Kingshott and Cercignani, 2009). Perfusion MRI measures tissue perfusion—that is, the delivery of blood via the microvascular system to tissue. Abnormalities in both diffusion and perfusion MRI are seen in many different neurodegenerative and psychiatric conditions such as those mentioned above. In summary, the committee recognizes that some of the imaging findings described could mediate symptoms associated with combat exposure (e.g., medical temporal lobe atrophy and PTSD). However, these MRI modalities are not disease-specific biomarkers in contrast to an imaging modality such as amyloid PET imaging (Klunk et al., 2004; Ikonomovic et al., 2008; Clark et al., 2011), which is specific for β-amyloid deposition in Alzheimer's disease.

The second limitation to attempting to identify imaging biomarkers for Gulf War illness is that specific environmental exposures were not habitually or reliably documented for every unit or for every veteran while deployed to the Persian Gulf region. To date, no imaging studies have identified a specific neuroimaging finding that might serve as a biomarker of exposure for a particular toxicant relevant to Gulf War illness (e.g., sarin, PB, or N,N-diethyl-meta-toluamide [DEET]). Some imaging studies have sought to identify an imaging signature of stress or of other mental health conditions such as PTSD. Although much work is being done in this area, it would be difficult many years after deployment to be sure that any neuroimaging anomalies were the result of deployment-related or combat-related stress rather than a subsequent stressful situation. More importantly, exposure to the stress of combat and putative exposure to environmental toxins are often comingled within study cohorts. This makes cause-and-effect inferences between environmental toxin exposure and specific imaging findings suspect.

The third limitation concerns methodological features of many imaging studies in this area. While structural MRI results are highly reproducible over time, derived MRI metrics (perfusion, diffusion, functional activation) are less so. Furthermore, voxel-based or multiple regions of interest-based analyses using atlases for anatomic labeling of brain regions can result in numerous comparisons in a given analysis. Large samples are needed to avoid statistical errors. Unfortunately, the sample sizes in many studies are small, which undermines the reliability of the results, particularly those for the more "noisy" imaging modalities. Another methodological issue is that participants in imaging studies are selected from larger cohorts. The criteria used to select participants for the imaging studies are rarely mentioned, which raises the question of participation bias. Moreover, participant selection biases likely differ from imaging study to study, thus contributing to interstudy inconsistencies. Because of these limitations, results within and across the neuroimaging studies are often conflicting and not reproducible, thereby calling into question any specific imaging signature or consequence of Gulf War illness.

Bierer et al. (2015) found decreased MD and increased FA in the right (but not left) cingulum bundle in Gulf War veterans with PTSD (n = 12) compared to those without PTSD (n = 8). Decreased MD and increased FA imply greater myelination and thus increased anatomic connectivity between brain areas served by these tracts. Bierer et al. also found that the presence of Gulf War illness in those with PTSD diminished these effects. The authors concluded that Gulf War illness is a distinct entity from PTSD, but unlike PTSD, Gulf War illness is associated with decreased central nervous system plasticity. The difficulty with this interpretation is that the inference about a specific effect of Gulf War illness on diffusion measures was based on comparing nine PTSD subjects who had CMI with three PTSD subjects sho did not have CMI. Much larger samples and evidence of independent replication of results would be needed to draw firm conclusions about pathophysiology. Rayhan and colleagues published a series of papers in 2013 comparing subsets of the same groups of Gulf War veterans with and without Gulf War

illness (determined by the Haley criteria). The groups were compared across many regions of interest on measures of diffusion MRI (Rayhan et al., 2013a) and task fMRI (Rayhan et al., 2013c,d). Various associations were found among the different Gulf War illness syndrome groups, but group sizes in some cases were less than 10 subjects. Small sample sizes coupled with failure to correct for multiple comparisons make it difficult to draw any conclusions.

Chao et al. (2015) compared diffusion MRI measures in 59 Gulf War veterans with predicted exposure to sarin/cyclosarin with 59 nonexposed veterans. Although prior research has linked FA changes to documented sarin exposure from the Tokyo subway sarin attack (Yamasue et al., 2007), the authors did not find FA changes in white matter in their predicted sarin-exposed group. They did report increased axial diffusivity among veterans with predicted exposure, but the interpretability of axial/radial diffusivity measures has been called into question (Wheeler-Kingshott and Cercignani, 2009), and Chao et al. did not correct for multiple comparisons.

Moffet et al. (2015) found fMRI activation differences between Gulf War veterans who met criteria for Haley's Gulf War illness syndrome 2 compared with controls during a verbal fluency task. The authors infer that the fMRI data provides support for the hypothesis that Gulf War illness syndrome is attributable to unique toxicant exposures during the Gulf War. However, the subjects performed worse on verbal fluency than the controls when the testing occurred outside the scanner. The fMRI findings are not a biomarker for a particular syndrome attributable to toxin exposure but are simply a manifestation of the fact that the control group performed better on verbal fluency tasks than the subject group. The same fMRI result would be expected when any two groups of subjects are compared where one group out performs the other on the cognitive task of interest. Hubbard et al. (2014) found fMRI activation differences between Gulf War veterans with and without Gulf War illness (Gulf War illness was determined using the Haley criteria). It is noteworthy thought that the same research group (Odegard et al., 2013) using a similar functional activation paradigm did not find fMRI differences among the three Gulf War illness syndrome groups.

Chao et al. (2011, 2010) examined brain volume and cognitive performance measures in a group of Gulf War veterans who may have been exposed to sarin or cyclosarin in comparison to matched Gulf War veterans who were not exposed. They found that grey and white matter brain volumes were reduced in the exposed group; however, there was no dose–response relationship between exposure and brain volume (which would be expected if the association were reliable). The exposed group performed worse on some psychometric tests but performed better on other tests. The results overall were inconsistent and do not conclusively support a relationship between exposure and either cognitive performance or reduced brain volumes. Li et al. (2011b) and Liu et al. (2011) published results of cerebral perfusion measured with arterial spin labeling MRI in response to physostigmine challenge in Gulf War veterans who met Haley's criteria for Gulf War illness syndromes 1, 2, or 3 and controls. Syndrome 2 and 3 subjects displayed reduced physostigmine effect on perfusion compared to controls, but syndrome 1 exhibited an increased physostigmine effect. The results were thus inconsistent among those who met the criteria for Gulf War illness. Moreover, it might be expected that syndromes 1 (impaired cognition) and 2 (confusion-ataxia) would be more similar than 2 and 3 (central neuropathic pain) because 1 and 2 both include impaired mental function, but the opposite was seen.

Other functional modalities in addition to imaging have been used. Tillman et al. (2010, 2012, 2013) assessed functional response by event-related potentials in groups of Gulf War illness syndromes. Various findings were reported, but sample sizes in some of the Gulf War illness syndrome groups were less than 10 subjects.

Conclusions

In summary, the imaging literature generally supports the established concept that MRI findings, such as evidence of brain atrophy, may be associated with chronic stress. But, the literature does not support the conclusion that any type of imaging signature is consistently associated with Gulf War illness, deployment to the Gulf War, or any specific Gulf War exposure. Thus, the committee does not find MRI abnormalities to be a valid biomarker of Gulf War illness disease.

The committee emphasizes that environmental exposures at the individual veteran level cannot be determined and therefore finds that conducting studies that seek or propose a cause-and-effect relationship between environmental exposures unique to Gulf War veterans (sarin, cyclosarin) and neuroimaging results is not advisable. Any studies of Gulf War veterans that use neuroimaging techniques should be adequately powered and should contain independent replication samples that are also adequately powered. This would help address the current state of the imaging literature, which is characterized by conflicting and nonreplicable results that make it difficult to draw coherent conclusions.

TABLE 4-11 Neurologic Conditions

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Volumes 4 and 8 Primary Studies						
Peripheral Neuropathy and Myopathy						
Davis et al., 2004 (Vol. 4)	Cross-sectional, prevalence, medical evaluation, exposure-specific component	1,047 GWVs vs 1,121 NDVs; 240 Khamisiyah-exposed GWVs vs 807 non-Khamisiyah-exposed GWVs	Distal symmetric polyneuropathy identified by nerve-conduction studya	GWVs vs NDVs: OR = 0.65 (95% CI 0.33–1.28); Khamisiyah-exposed GWVs vs non-Khamisiyah-exposed GWVs: OR = 1.04 (95% CI 0.25–4.37)	Excludes coexisting conditionsb	Low participation rate: 53% in deployed veterans, 39% in nondeployed veterans
Rose et al., 2004; Sharief et al., 2002 (Vol. 4)	Case-control	49 symptomatic deployed UK veterans vs 26 healthy deployed UK veterans, 13 symptomatic Bosnia deployed veterans, 22 symptomatic NDVs	Nerve-conduction studies, quantitative sensory and autonomic testing, concentric needle and single-fiber, electromyography, ischemic forearm exercise test, subanaerobic bicycle exercise test, muscle biopsy	No significant differences between symptomatic deployed and nondeployed veterans, except deployed veterans had increased lactate production in bicycle exercise test		
Kelsall et al., 2005 (Vol. 8)	Cross-sectional survey	1,382 Australian male GWVs, 1,376 male NDVs frequency	Self-reported neurologic symptoms corroborated during neurological examination; SF-12;	Lower limb neurological type symptoms and signs: OR = 1.6 (95% CI 1.0–2.7) Neuropathy Score: GWV (2.0, sd = 4.3) vs NDVs (2.0, sd = 4.7)	Age, rank, service type, current marital status, highest level of education,	Exposure data self-reported; response rate 80.5% for GWVs, 56.8% for NDVs

Study	Design	Population	Outcomes	Results	Adjustments	Comments
		matched by age and service type (Same study population as Kelsall et al., 2004a,b)	modified NIS	RoM = 1.1 (95% CI 0.9–1.3) Association of neurological symptoms in self-reported nonexposed compared to exposed: PB (RoM = 1.5, 95% CI 1.2–1.8) Antibiological warfare tablets (RoM = 1.8, 95% CI 1.3-2.5) Solvents (RoM = 1.8, 95% CI 1.4–2.2) Pesticides (RoM = 1.7, 95% CI 1.4–2.0) Insect repellents (RoM = 1.3, 95% CI 1.1–1.5) No association with self-reports of immunizations or chemical exposure	alcohol consumption, and history of diabetes	
Amyotrophic Lateral Sclerosis						
Horner et al., 2003 (Vol. 4)	Retrospec-tive cohort	All active, GWVs (1990–1991) compared with NDVs	ALS	All deployed forces, significant increased risk of ALS (RR = 1.92, 95% CI 1.29–2.84)	Age-adjusted average, annual 10-year incidence; attributable risk	Case ascertainment through screening of VA and DoD medical databases and benefit files (and TriCare) by ICD-9 code for ALS or riluzole use; extensive recruitment efforts
Coffman et al., 2005 (Vol. 4)	Capture–recapture reanalysis of Horner et al., cohort	See Horner et al., 2003	ALS	Found no under-ascertainment of ALS cases among deployed	Log-linear models; sample coverage; ecologic models	Possible undercounts not likely to substantively affect results
Horner et al., 2008	Retrospectiv e cohort,	All active, Gulf War	ALS	Deployed (48 cases) vs nondeployed (76 cases), no	Age-adjusted average, annual	Small number of cases and short follow-up

Study	Design	Population	Outcomes	Results	Adjustments	Comments
(Vol. 8)	follow-up from 1991–2001 (follow-up of Horner et al., 2003)	deployed military personnel (n = 696,118), compared with NDVs		significant difference in SIR during additional follow-up period Similar percentage of young onset between deployed (69%) and controls (64%)	10-year incidence; attributable risk	period limit the ability of the study to determine long-term trends
Neurobehavioral and Neurocognitive Studies						
David et al., 2002 (Vol. 4)	Case-control, clinical evaluations	200 male UK GWVs, 54 Bosnia-deployed, 78 era nondeployed veterans randomly selected from larger cohort of UK veterans who participated in earlier postal survey (see Unwin et al., 1999)	WAIS-R scaled scores: Vocabulary, Digit span, Arithmetic, Similarities, Picture arrangement, Block design, Object assembly, Digit symbol, PASAT, Sustained attention to response task, Stroop, Trail-making test, A & B WMS: Logical memory, Verbal paired associates, Camden recognition memory test, Purdue pegboard	GWVs had significantly lower scores on 5 cognitive tests after demographic confounder and LSD corrections: Digit symbol Trail-making Stroop PASAT Verbal associates After final Bonferroni adjustments for multiple comparisons and BDI, only the results of the Purdue pegboard remained significantly different	ANCOVA adjusted for education, age, NART, BDI; multiple comparison adjustment for least significant difference procedure and Bonferroni adjustments	Careful treatment of potential confounders, such as depression, mood, IQ, education Examiners were blinded
Proctor et al., 2003 (Vol. 4)	Cross-sectional	143 male Danish GWVs, 72 male NDVs randomly	WAIS-R Information subscale, continuous performance test, trail making,	No overall differences in neuropsychologic domains, significant test differences in domains ($p \leq 0.05$) for CVLT and WCST	MANCOVA by neuropsychologic domain, adjusted for age	Response rate 75%

Study	Design	Population	Outcomes	Results	Adjustments	Comments
		selected from 84% and 58% of total Danish armed forces deployed and nondeployed, respectively, at time of Gulf War	WCST, Purdue pegboard, WAIS-R block design, CVLT, WMS visual reproductions, TOMM; individually administered tests except in computer-based NES; blinded examiners			
Storzbach, 2001 (Vol. 4)	Case-control	239 randomly selected male and female GWVs with symptoms vs 112 deployed with no symptoms; case = one of memory loss, confusion, inability to concentrate, mood swings, somnolence, gastrointestinal distress, fatigue, muscle and joint pain, skin or mucous membrane lesions lasting 1 month or	Symbol digit Serial digit learning ODTP Selective attention test Digit span Simple reaction time BARS computer-based testing system Blinded examiners	Cases significantly worse than controls on: Digit span backward Simple reaction time ODTP Errors Latency (including a slow group of 13% of sample with scores > 2 sd slower than control mean latency) PCA showed the slow ODTP (slow case in 1999) were responsible for group differences in neurobehavioral performance; 2 of 354 excluded for possible poor motivation because of excess errors in ODTP	ANCOVA, adjusted for age, sex, and AFQT, but effect was small so t-tests were used; Bonferroni correction for multiple comparisons	

Study	Design	Population	Outcomes	Results	Adjustments	Comments
		longer, starting during or after service in gulf, and present during 3 months before questionnaire received				
Volume 10 Primary Studies						
Amyotrophic Lateral Sclerosis						
Kasarkis et al., 2009	Cohort study; medical records review	All veterans on active duty between 1990–1991 (GWVs = 696,118; NDVs = 1,786,215) 109 ALS/ MND cases diagnosed 1990–2002	ALS/MND verified by medical records, World Federation of Neurology case definition used Disease characteristics abstracted from medical records	43 cases GWVs; 66 cases NDVs by DMDC records (55 cases deployed; 53 nondeployed by self-report) Age of disease onset, race, site of onset, family history not different by deployment group Median survival time less in deployed cases (40 vs 57 months, HR = 0.62, 95% CI 0.4–0.96)	Survival analyses adjusted for age and site of onset	Derivative of Horner et al., 2003, (28 additional cases) Active and passive case ascertainment methods used All cases were male Discrepancy between DMDC recorded and self-reported deployment (43 vs 55)
Multiple Sclerosis						
Wallin et al., 2014	Cohort study	387 GWV cases and 1,454 NDV cases of MS and clinically isolated syndromes among veterans on	MS incidence rates MS diagnosed using 2005 McDonald criteria; neuromyelitis diagnosed with Wingerchuk et al., 2006 criteria; other demyelinating	Deployment was protective of MS risk and all demyelinating disorders (RR = 0.7, 95% CI 0.6–0.8) Risk associated with Khamisiyah exposure was not significant (RR = 1.1, 95% CI 0.8–1.5; 65 exposed cases)	Age, race, sex, or service branch	Derivative of Wallin et al., 2012 Explores possibility of health warrior/soldier effect on explaining protective effect of seemingly adverse set of exposures

Study	Design	Population	Outcomes	Results	Adjustments	Comments
		active duty 1990–1991 (GWVs = 696,118; NDVs = 1,786,215).	disease includes clinically isolated syndromes and possible MS Sarin and cyclosarin exposure provided by DoD Khamisiyah plume modeling			
Neurobehavioral and Neurocognitive Studies						
Ishoy et al., 2004	Cross-sectional; clinical examination in 1997	686 Danish GWVs (83.6% of all deployed); 231 NDVs	Physician-administered neuropsychological questionnaire; CATSYS Test System: hand pronation/ supination; finger tapping; reaction time; tremor test; and sway test	Statistically significant difference between GWVs and NDVs for concentration, headache, balance disturbance or dizziness, abnormal fatigue, and problems sleeping all night CATSYS test system results were not statistically significant between the two groups for 23 of 26 test results ($p \leq 0.05$); 3 significant ones represented only small differences	Adjusted for age, gender, and occupation	84% participation rate among GWVs, 58% among NDVs

NOTE: AFQT = Armed Forces Qualifying Test; ALS = amyotrophic lateral sclerosis; ANCOVA = analysis of covariance; BARS = Behavioral Assessment and Research System; BDI = Beck Depression Inventory; CATSYS = Coordination Ability Test System; CI = confidence interval; CVLT = California Verbal Learning Test; DMDC = Defense Manpower Data Center; DoD = Department of Defense; GWV = Gulf War veteran; HR = hazard ratio; ICD = International Classification of Diseases; LSD = least significant difference; MANCOVA = multivariate analysis of variance; MND = motor neuron disease; MS = multiple sclerosis; NART = National Adult Reading Test; NDV = nondeployed veteran; NHS = National Health Service; NIS = Neuropathy Impairment Score (Mayo Clinic version); ODTP = Oregon Dual Task Procedure; OR = odds ratio; PASAT = Paced Auditory Serial Addition Test; PB = pyridostigmine bromide; PCA = principal-components analysis; RoM = ratio of means; sd = standard deviation; RR = risk ratio; SF-12 = 12-item Short Form Health Survey; SF-36 = 36-Item Short Form Health Survey; SIR = standardized incidence ratio; TOMM = Test of Memory Malingering; UK = United Kingdom; VA = Department of Veterans Affairs; WAIS =

Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale.

[a]Although the study defined distal symmetric polyneuropathy as distal sensory or motor neuropathy identified on basis of neurologic examination, nerve conduction study, or both, the committee defined it by nerve-conduction study alone.

[b]Alcohol dependence, diabetes mellitus, renal insufficiency, hypothyroidism, AIDS/HIV, collagen vascular disease, and neurotoxic medications.

RESPIRATORY SYSTEM CONDITIONS

As noted in previous Gulf War and Health reports (IOM 2006b, 2010), respiratory conditions such as asthma, bronchitis, chronic obstructive pulmonary disease (COPD), and various symptoms consistent with respiratory disease, such as wheezing and shortness of breath, have consistently been self-reported more frequently by deployed Gulf War veterans than era veterans. Exposures of concern during deployment include smoke from oil-well fires, high levels of ambient dust, pesticide sprays, and nerve gas exposure. Lung cancer is discussed in the section on cancer. All primary studies of conditions of the respiratory system are summarized in Table 4-12 at the end of this section.

Summary of Volumes 4 and 8

Volume 4 presented five primary studies (Eisen et al., 2005, Gray et al., 1999a; Ishoy et al., 1999b; Karlinsky et al., 2004; Kelsall et al., 2004b) that represented four cohorts from three countries. Those studies examined associations of respiratory outcomes with deployment to the Gulf War region. Outcomes were, in part, determined on the basis of pulmonary function measures or respiratory disease diagnoses. None of those studies reported any positive associations with Gulf War Service. Numerous secondary studies were reviewed that relied on self-reported respiratory symptoms, and the overwhelming majority of these studies found that deployed veterans report higher levels of respiratory symptoms and respiratory illnesses than nondeployed veterans.

The Volume 4 committee also reviewed objective measures of respiratory conditions associated with specific exposures experienced by Gulf war veterans during their deployment. Three studies used the same objective exposure measure and methods to estimate exposure to smoke from oil-well fires, but no associations were detected for doctor-assigned diagnoses of asthma, respiratory health outcomes, and hospitalization for asthma, acute bronchitis, chronic bronchitis, or emphysema. One study (Gray et al., 1999b) found an association between modeled exposure to nerve agents at Khamisiyah and a small increase in postwar hospitalization for respiratory system disease. However, that study had several limitations including likely exposure misclassification, failure to control for tobacco smoking, lack of a clear dose–response pattern, and there appeared to be little biologic plausibility for effects on the respiratory system. A second study of nerve agent exposure and pulmonary function measures found no association between the two (Karlinsky et al., 2004). The Volume 4 committee noted that, with respect to nerve agents at Khamisiyah, no study that used valid objective estimates of exposure found statistically significant associations with pulmonary function measures or physician-diagnosed respiratory disease.

Based on one additional primary (Smith et al., 2006) and four secondary studies (including one study that assessed Khamisiyah-exposed veterans specifically), the Volume 8 committee also found that studies of Gulf War veterans based on self-reported symptoms and self-reported diagnoses have frequently, but inconsistently, shown an excess of respiratory conditions. However, there appears to be no increase in respiratory disease among Gulf War veterans when examined with objective measures of disease. Pulmonary function studies have shown no significant excess of lung function abnormalities among Gulf War veterans. *Therefore, the Volume 8 committee concluded that there was insufficient/inadequate evidence to determine*

whether an association exists between deployment to the Gulf War and respiratory disease. The committee also concluded that there was limited/suggestive evidence of no association between deployment to the Gulf War and decreased lung function in the first 10 years after the war.

New Literature

The Volume 10 committee did not identify any new primary studies of Gulf War veterans that assessed respiratory conditions.

Secondary Studies

The Volume 10 committee identified three secondary studies. Sim et al. (2015) reported on the Australian Gulf War Veterans' Follow Up Health Study, conducted between 2011 and 2013 (this study was a follow-up to the Kelsall et al., 2004b, baseline study discussed in Volumes 4 and 8). This study assessed the entire Australian Gulf War cohort 10 years after the 2000–2002 baseline study and 20 years after the war. Results were adjusted for age, rank category, and service branch, but not for smoking. Of the 1,456 eligible deployed veterans, 715 participated in the study and 675 of the 1,449 nondeployed veterans formed the comparison group. Respiratory symptoms were based on self-reports and on self-reports of doctor-diagnosed respiratory symptoms. Deployed veterans were significantly more likely to report morning cough (RR = 1.67, 95% CI 1.26–2.23), wheeze (RR = 1.44, 95% CI 1.15–1.80), morning sputum (RR = 1.38, 95% CI 1.10–1.74), and daytime or nighttime cough (RR = 1.36, 95% CI 1.09–1.70). They were also more likely to report a doctor-diagnosis or treatment for sinus problems (RR = 1.51, 95% CI 1.07–2.15) and pneumonia (RR = 1.87, 95% CI 1.03–3.39). Deployed veterans were also more likely to report, although not significantly so, a doctor-confirmed diagnosis of asthma, chronic bronchitis, emphysema, or COPD.

Li et al. (2011a) conducted a 10-year follow-up survey of U.S. Gulf War deployed (n = 5,469) and nondeployed veterans (n = 3,353) who had also participated in a 1995 VA National Health Survey. Compared with nondeployed veterans, deployed veterans in 2005 were less likely to report the persistence of chronic asthma (RR = 0.76, 95% CI 0.59–0.97), although they did have a nonstatistically significant increased risk of a new onset of it (RR = 1.26, 95% CI 0.94–1.68). The risk ratios were adjusted for age in 2005, gender, race, rank, service branch, service type, BMI, and current cigarette smoking.

Dursa et al. (2016) reported results of the third survey wave of the cross-sectional National Health Study of Persian Gulf War Era Veterans. The wave 3 survey (discussed in greater detail in Chapter 3), conducted in 2012–2013 via mail, website, or a computer-assisted telephone interview, asked 8,104 Gulf War deployed and 6,148 era veterans to indicate whether a doctor had ever told them they had a medical condition and then whether the condition had been present in the previous 4 weeks. There was a statistically significant difference between the deployed and era veterans in self-reports of asthma (10.2% vs 9.0%; OR = 1.22, 95% CI 1.04–1.44) and COPD (8.4% vs 6.3%; OR = 1.48, 95% CI 1.23–1.78). The OR was adjusted for age, race, sex, BMI, smoking status, service branch, and unit component.

Other Related Studies

VA provided a health care use report for Gulf War deployed and era veterans who sought care in VA facilities from October 2001 to December 2013. The report presented the prevalence of diagnoses of diseases by ICD-9 code categories, including diseases of the respiratory system (ICD-9 categories 460–519) (Table 4-13). 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. A total of 286,995 Gulf War deployed and 296,635 era veterans received treatment at VA over the approximately 11-year period (VA, 2014a,b). These VA health care users represent 46% of all deployed Gulf War veterans and 36% of all nondeployed era veterans.

TABLE 4-13 Ten Most Frequent Respiratory Disease Diagnoses for Deployed and Nondeployed Gulf War Veterans Seeking Health Care in VA Between 2002 and 2013

Diagnosis	Deployed N = 105,481 (%)	Nondeployed N = 97,539 (%)
Allergic rhinitis	39.1	39.2
Acute upper respiratory infections of multiple or unspecified sties	28.8	29.6
Chronic sinusitis	22.6	22.6
Asthma	16.7	16.5
Acute bronchitis, bronchiolitis	13.6	13.9
Acute sinusitis	13.6	14.1
Pharyngitis, acute	13.2	13.3
Chronic airway obstruction, not elsewhere classified	12.4	12.6
Bronchitis, not specified as acute or chronic	12.2	12.4
Chronic pharyngitis, nasopharyngitis	8.8	8.8

SOURCE: VA (2014a,b).

Conclusions

The three new secondary studies provide mixed results. In the Australian study, there was a significant increase in self-reported respiratory symptoms such as cough in deployed compared with nondeployed Gulf War veterans. However, two of the three studies showed no increase in the risk of asthma or COPD (Sim et al., 2015; Li et al., 2011a); whereas, the VA survey found a slight increase in the risk of asthma and a slightly greater risk of having COPD (Dursa et al., 2016). All of these studies relied on self-reports of diagnoses.

The committee finds that, because the respiratory system is a common portal for exposure, should continued surveillance of respiratory conditions in Gulf War veterans be conducted, the studies need to adjust for smoking if the data are to be informative.

Therefore, the Volume 10 committee concludes that there is insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and respiratory disease. The committee concludes that there is limited/suggestive evidence of no association between deployment to the Gulf War and decreased lung function.

TABLE 4-12 Conditions of the Respiratory System

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Eisen et al., 2005 (Vol. 4)	Population-based, cross-sectional, prevalence, medical evaluation	1,061 U.S. GWVs vs 1128 NDVs	Self-reported asthma, bronchitis, or emphysema; obstructive lung disease (history of disease or symptoms plus use of bronchodilators or 15% improvement in FEV_1 after bronchodilator use)	Asthma, bronchitis, or emphysema: OR = 1.07 (95% CI 0.65–1.77) Obstructive lung disease: OR = 0.91 (95% CI 0.52–1.59)	Age, sex, race, years of education, smoking, duty type, service branch, rank	Low participation rates, especially among nondeployed
Karlinsky et al., 2004 (Vol. 4)	Cross-sectional, medical evaluation	1,036 U.S. GWVs vs 1103 NDVs	PFT results classified into five categories: normal, nonreversible obstruction, reversible obstruction, restrictive, small-airways obstruction	No association of PFT-based classifications with deployment status, nor with exposure to nerve agents at Khamisiyah based on 2002 DoD exposure models	No adjustment for smoking or other confounders	Description of sampling strategy inadequate to evaluate bias; no explanation of "matching" or control of matching in analysis
Gray et al., 1999a (Vol. 4)	Cross-sectional, medical evaluation	527 GWVs vs 970 NDVs from 14 U.S. Navy Seabees commands	Cough; shortness of breath; FVC (L); FEV_1 (L)	Cough : OR = 1.8 (95% CI 1.2–2.8) Shortness of breath: OR = 4.0 (95% CI 2.2–7.3) FVC (L): 4.96 vs 4.99, p = 0.77 FEV_1 (L): 4.05 vs 4.04, p = 0.81	Age, height, race, smoking status	No use of modeled oil-fire exposures
Kelsall et al., 2004b (Vol. 4)	Cross-sectional, medical evaluation	1,456 Australian GWVs vs 1588 NDVs	Asthma; bronchitis; FEV_1/FVC% < 70%	Asthma: OR = 1.2 (95% CI 0.8–1.8); Bronchitis: OR = 1.9 (95%	Service type, rank, age, education,	Generally well done; substantial potential for selection bias

Study	Design	Population	Outcomes	Results	Adjustments	Comments
				CI 1.2–3.1); $FEV_1/FVC < 70\%$: OR = 0.8 (95% CI 0.5–1.1); FVC, but not FEV_1, associated with self-report of oil-well fire exposure	marital status	(response rates: GWVs 81% vs NDVs 57%); no use of modeled oil-well fire exposures
Ishoy et al., 1999b (Vol. 4)	Cross-sectional, population-based, medical evaluation	686 peacekeeping Danish GWVs vs 231 NDVs	Shortness of breath; FVC; FEV_1; peak flow	14% vs 3.5% Percent of predicted: FVC 100.7 vs 100.7, NS FEV_1 95.6 vs 96.4, NS peak flow 94.0 vs 92.8, NS	None	Appropriate population-based controls but differential participation: 84% deployed vs 58% nondeployed; smoking histories similar in deployed and nondeployed
Smith et al., 2006 (Vol. 8)	Hospitalizations cohort study (cohort data from DMDC)	Active-duty personnel with a single deployment to: Gulf War theater (n = 455,465); Southwest Asia peacekeeping mission, 1991–1998 (n = 249,047); Bosnia, 1995–1998 (n = 44,341)	Postdeployment hospitalization events (1991–2000) for an ICD-9-CM diagnosis of respiratory disease (140–208)	Veterans of Bosnia compared to GWV: HR = 0.73 (95% CI 0.63–0.84) Veterans of Southwest Asia compared to GWV: HR = 1.08 (95% CI 1.00–1.16)	Sex, age, marital status, pay grade, race/ethnicity, service branch, occupation, and predeployment hospitalization; time-dependent covariate to account for changing hospitalization methods, diagnostic criteria, and procedures	Active-duty personnel only; hospitalizations at DoD facilities only

Studies of Respiratory Outcomes Specifically Associated with Modeled Exposure to Oil-Well Fires

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Cowan et al., 2002 (Vol. 4)	Case-control study of exposure to smoke from oil-well fires; DoD registry, Army only	873 GWVs with asthma vs 2,464 controls	Physician-assigned diagnosis of asthma 3–6 years after war	Self-reported exposure: OR = 1.56 (95% CI 1.23–1.97) Cumulative modeled exposure: OR = 1.24 (95% CI 1.00–1.55) for intermediate cumulative modeled exposure; OR = 1.40 (95% CI 1.11–1.75) for high exposure Number of days at > 65 $\mu g/m^3$: OR = 1.22 (95% CI 0.99–1.51) for 1–5 days; OR = 1.41 (95% CI 1.12–1.77) for 6–30 days	Sex, age, race, military rank, smoking history, self-reported exposure	Effect seen in former smokers and never-smokers, but not current smokers. Modeled exposure rather than only self-reported exposure; however, self-selected population; no specified criteria for asthma diagnosis and no pulmonary function data; pre-exposure asthma status unknown
Lange et al., 2002 (Vol. 4)	Cross-sectional study of exposure to smoke from oil-well fires; derived from cohort study	1,560 Iowa veterans	Asthma symptoms; bronchitis symptoms; structured interviews conducted 5 years after the war	For modeled exposure, ORs for quartiles of exposure, 0.77–1.26 with no dose–response relationship; for self-reported exposure, asthma ORs = 1.77–2.83, bronchitis ORs = 2.14–4.78	Sex, age, race, military rank, smoking history, military service, level of preparedness for war	Modeled exposure rather than only self-reported exposure, population-based sample Symptom-based case definition of bronchitis and asthma
Smith et al., 2002 (Vol. 4)	DoD hospitalizations 1991–1999; exposure modeling for oil-well fire smoke	405,142 active-duty Gulf War veterans	ICD-9-CM codes: Asthma Acute bronchitis Chronic bronchitis Emphysema Respiratory conditions due to chemical fumes and	Exposed vs nonexposed: OR = 0.90 (95% CI 0.74–1.10) OR = 1.09 (95% CI 0.62–1.90) OR = 0.78 (95% CI 0.38–1.57) OR = 1.36 (95% CI 0.62–2.98) OR = 0.71 (95% CI 0.23–2.17)	"Influential predictors" of $p <$ 0.15 included in analyses	Objective measure of disease not subject to recall bias; no issues with self-selection; however, only DoD hospitals, only active duty, no information on smoking or other confounders related to respiratory symptoms Asthma and chronic bronchitis do not often

Study	Design	Population	Outcomes	Results	Adjustments	Comments
			vapors			require hospitalization
			Other respiratory diseases	OR = 1.45 (95% CI 0.86–2.46)		
Study of Respiratory Outcomes Specifically Associated with Exposure to Khamisiyah Nerve Agent						
Gray et al., 1999b (Vol. 4)	DoD hospitalizations 1991–1995, exposure to nerve agents at Khamisiyah based on 1997 DoD exposure models	Not exposed (n = 224,804), uncertain low-dose exposure (n = 75,717), exposed (n = 48,770)	Respiratory system disease (vs not exposed):		Sex, age group, prewar hospitalization, race, service type, marital status, pay grade, occupation	Probable substantial exposure misclassification as models were revised, lack of a clear dose–response pattern, little biologic plausibility given that no effect was seen for nervous system conditions
			Uncertain low dose	OR = 0.92 (95% CI 0.85–0.99)		
			< 0.013 mg-min/m^3	OR = 0.90 (95% CI 0.77–1.04)		
			0.013–0.097 mg-min/m^3	OR = 0.89 (95% CI 0.79–1.02)		
			0.097–0.514 mg-min/m^3	OR = 1.26 (95% CI 1.05–1.51)		

NOTE: CI = confidence interval; DMDC = Defense Manpower Data Center; DoD = Department of Defense; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GWV = Gulf War veteran; HR = hazard ratio; ICD = International Classification of Diseases; MRR = mortality rate ratio; NS = not significant; OR = odds ratio; PFT = pulmonary function test; UK = United Kingdom; U.S. = United States.

GASTROINTESTINAL SYSTEM CONDITIONS

Digestive disorders may be functional, structural, or in some cases combinations of both (see *Gulf War and Health, Volume 6*, for a description of functional and structural digestive disorders). The functional gastrointestinal (GI) disorders, such as irritable bowel syndrome (IBS) or functional dyspepsia, are conditions without pathology or clear structural change—that is, recurrent or prolonged clusters of symptoms that occur together. GI conditions, sometimes called "organic" or structural conditions, such as peptic ulcer and inflammatory bowel disease (that is, ulcerative colitis and Crohn's disease), are characterized by morphological abnormalities seen on x-ray, endoscopy, or through laboratory tests. All primary studies for conditions of the gastrointestinal system are summarized in Table 4-14 at the end of this section.

Summary of Volumes 4 and 8

The Volume 4 committee reviewed three primary studies of digestive system disorders, two of which analyzed hospitalization data. In one report (Eisen et al., 2005), dyspepsia was diagnosed on the basis of in-person interviews and was statistically significantly associated with deployment; however, the Volume 8 committee noted that some cases of dyspepsia may have been misdiagnosed given the terminology used by the authors. One study by Gray et al. (1996) found no excess hospitalizations for conditions of the digestive system for deployed or nondeployed veterans, although in a later study they found an increase in hospitalizations for digestive system conditions at VA hospitals but not in other hospital systems for deployed versus nondeployed veterans (Gray et al., 2000). Two secondary studies showed that deployed veterans more frequently reported gastrointestinal symptoms than nondeployed veterans (Sostek et al., 1996; Ishoy et al., 1999a,b). The Volume 4 committee noted that gastrointestinal disturbances in Gulf War-deployed veterans seem to be linked to contaminated water and burning of animal waste.

The Volume 8 committee found in numerous studies that Gulf War veterans self-reported more GI symptoms than nondeployed veterans (Kang et al., 2000; Kelsall et al., 2004a; Proctor et al., 1998; Simmons et al., 2004; Sostek et al., 1996; Unwin et al., 1999). The primary study by Sostek et al. (1996) used survey questions that were highly specific for functional GI disorders and that met the Rome III criteria for IBS. The study found statistically significant increases in the reporting of symptoms consistent with IBS and other functional GI disorders in deployed veterans compared with nondeployed veterans. All of the secondary studies identified by the committee found that deployed veterans reported more GI symptoms than their nondeployed counterparts, but the studies were limited because their methods are insufficient to determine a clear association between deployment and the onset of a functional disorder—diagnosed by standard Rome criteria—or of a structural disorder. The committee noted that the diagnosis of structural GI conditions should be validated by medical records because physicians may place an organic label on a patient's symptoms (e.g., gastritis or peptic ulcer) without performing the necessary diagnostic studies.

The Volume 8 committee found limitations in the epidemiologic body of evidence for GI disorders, mostly related to methods of effect assessment. These limitations included self-reporting of GI symptoms that did not fulfill the criteria for diagnosing a functional GI disorder, inability to determine the degree to which the gastrointestinal symptoms are specific to IBS and

other functional GI disorders or are part of a larger spectrum of illness (specifically, Gulf War illness), lack of determination of the presence of medical and psychosocial comorbidities, and a lack of adequate medical diagnostic testing to identify a GI structural disease. Nevertheless, taken together, the Volume 8 committee found that the overall pattern of symptoms reported in the few primary and numerous secondary studies confirmed an association between deployment to the Gulf War and functional GI symptoms, including abdominal pain, diarrhea, nausea, and vomiting, and a few studies exist that provide presumptive data to allow standardized diagnosis of functional GI disorders. These studies were strengthened by physiologic and mechanistic data for veterans with IBS, with particular reference to new evidence for preexisting acute gastroenteritis as a predictive factor in postinfectious IBS and dyspepsia. The Volume 8 committee recommended that further studies be conducted to determine the role of prior acute gastroenteritis among deployed service members in the development of functional GI disorders. *Therefore, the Volume 8 committee concluded that there was sufficient evidence for an association between deployment to the Gulf War and gastrointestinal symptoms consistent with functional GI disorders such as irritable bowel syndrome and functional dyspepsia. The committee also concluded that there was inadequate/insufficient evidence to determine whether an association exists between deployment to a war zone and the development of structural gastrointestinal conditions.*

New Literature

The Volume 10 committee did not identify any new studies that met its criteria for a primary study. One study of Australian veterans and preliminary results on the VA's follow-up survey of U.S. Gulf War veterans were considered to be secondary studies.

Secondary Studies

Sim et al. (2015) conducted the Australian Gulf War Veterans' Follow Up Health Study between 2011 and 2013 to assess the entire Australian Gulf War cohort 10 years after the 2000–2002 baseline study and 20 years after the war. Results were adjusted for age, rank category, and service branch, but not for smoking. Of the 1,456 eligible deployed veterans, 715 participated in the study and 675 of the 1,449 nondeployed veterans made up the comparison group. The prevalence of GI conditions was based on self-reports and on self-reports of doctor-diagnosed conditions. There were no statistically significant differences in reporting of doctor-diagnosed GI conditions. More deployed than nondeployed veterans reported having polyps in the bowel (RR = 1.34, 95% CI 0.96–1.88). There were statistically significantly more deployed veterans who met the Rome III criteria for IBS based on self-reported symptoms than nondeployed veterans (13% vs 8%; RR = 1.64, 95% CI 1.18–2.27).

The committee also considered the results from Dursa et al. (2016) on the third wave of the National Health Study of Persian Gulf War Era Veterans The wave 3 survey (discussed in greater detail in Chapter 3), conducted in 2012–2013 via mail, website, or a computer-assisted telephone interview, asked 8,104 deployed and 6,148 Gulf War era veterans to indicate whether a doctor had ever told them they had a medical condition and then whether the condition had been present in the previous 4 weeks. There were statistically significant differences between the deployed and era veterans in the weighted prevalence of self-reports of IBS (24.4% vs 14.3%; OR = 2.1, 95% CI 1.79–2.45), gastritis (20.2% vs 14.3%; OR = 1.59, 95% CI 1.35–1.73), and functional dyspepsia based on the ROME criteria (27.7% vs 15.9%; OR = 1.94, 95% CI 1.75–2.17). The ORs were adjusted for age, race, sex, BMI, smoking status, service branch, and unit

component. Self-reports of hepatitis and cirrhosis were also included in the survey, but the odds of either condition were not statistically different between deployed and era veterans (Dursa et al., 2016).

Other Related Studies

VA provided a health care use report for Gulf War deployed and era veterans who sought care in VA facilities from October 2001 to December 2013. The report presented the prevalence of diagnoses of diseases by ICD-9 code categories, including diseases of the digestive system (ICD-9 categories 520–579) (Table 4-15). 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. A total of 286,995 Gulf War deployed and 296,635 era veterans received treatment at VA over the approximately 11-year period (VA, 2014a,b). These VA health care users represent 46% of all deployed Gulf War veterans and 36% of all nondeployed era veterans.

TABLE 4-15 Ten Most Frequent Diagnoses of Diseases of the Digestive System for Deployed and Nondeployed Gulf War Veterans Seeking Health Care in VA Between 2002 and 2013

Diagnosis	Deployed N = 127,786 (%)	Nondeployed N = 117,565 (%)
Diseases of esophagus	50.4	49.1
Other diseases of the teeth, supporting structures	32.3	33.0
Diseases of hard tissues of teeth	28.1	28.5
Gingival and periodontal diseases	25.6	26.2
Functional digestive disorders, NEC	15.7	13.8
Other hernia of abdominal cavity without obstruction or gangrene	10.4	9.8
Other disorders of intestine	10	9.8
Gastrointestinal hemorrhage	9.5	9.2
Diverticula of intestine	8.8	10.1
Diseases of pulp, periapical tissues	7.9	8.0

SOURCE: VA (2014a,b).

In another analysis of the second wave of the VA's National Health Survey of Gulf War Veterans, Coughlin and colleagues (2011a) found that among 6,111 Gulf War deployed and 3,859 era veterans, deployed veterans, regardless of their weight status (underweight, normal weight, overweight, or obese), self-reported more physician-diagnosed cirrhosis of the liver, hepatitis, and gastritis than nondeployed veterans. No information was provided on diet or physical activity. Further assessment of these veterans found that self-reported GI outcomes were more prevalent in both deployed and nondeployed veterans with problem drinking. Unadjusted percentages of veterans reporting cirrhosis, hepatitis, and gastritis are presented in Table 4-16 (Coughlin et al., 2011b). Problem drinking was determined based on affirmative answers to questions about problem or hazardous drinking in the previous 6 months. No modeling or statistical testing was reported pertaining to these outcomes.

TABLE 4-16 Unadjusted Percentages of Self-Reported Physician-Diagnosed Outcomes Reported in Deployed vs Nondeployed Gulf War Veterans

	Without Problem Drinking	Problem Drinking
Cirrhosis of the liver	8.1% vs 6.3%	9.9% vs 6.9%
Hepatitis	10.4% vs 8.9%	13.3% vs 9.8%
Gastritis	26.8% vs 17.6%	30.3% vs 21.7%

SOURCE: Coughlin et al. (2011b).

Conclusions

The Volume 8 committee found there was sufficient evidence for an association between deployment to the Gulf War and gastrointestinal symptoms consistent with functional GI disorders such as IBS and functional dyspepsia. Two new secondary studies provide additional support for this conclusion by reporting increased rates of IBS among deployed veterans; however, they are based on self-reported information.

The Volume 8 committee also concluded that there was inadequate/insufficient evidence to determine whether an association exists between deployment to a war zone and the development of structural gastrointestinal conditions. Little new literature was available to assess the risks of structural gastrointestinal disease, but the literature did not suggest increased risks among deployed veterans. The committee finds that given the aging of the population of Gulf War veterans and the unlikelihood that new gastrointestinal conditions will develop 25 years after the Gulf war that are attributable to their Gulf War service, it is doubtful that further assessments will show increased risk of these conditions.

Therefore, the Volume 10 committee concludes that there is sufficient evidence for an association between deployment to the Gulf War and gastrointestinal symptoms consistent with functional gastrointestinal disorders such as irritable bowel syndrome and functional dyspepsia. The committee also concludes that there is inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and the development of structural gastrointestinal conditions.

TABLE 4-14 Conditions of the Gastrointestinal System

Study	Study Design	Population	Outcomes	Results	Adjustments	Comments
Eisen et al., 2005 (Vol. 4)	Cross-sectional, prevalence	1,061 GWVs vs 1,128 NDVs	Physician evaluation, questionnaire for dyspepsia; GI symptoms and medical conditions reported from earlier survey	Dyspepsia (OR = 1.87, 95% CI 1.16–2.99); self-reported gastritis (OR = 1.57, 95% CI 0.88–2.78)	Age, sex, race, smoking, duty type, service branch, rank, years of education	Limited by low participation rate, length of time since war; weak diagnostic criteria
Gray et al., 1996 (Vol. 4)	Retrospective cohort study (hospitalization records)	DoD hospitals: 547,076 GWVs; 618,335 NDVs	Digestive system diseases	All ORs < 1.0	Hospitalization rates and rate ratios adjusted for age, sex; multiple logistic-regression models adjusted for all observed demographic differences between groups	Data reflect only hospitalization experience of persons who remained on active duty through September 1993
Gray et al., 2000 (Vol. 4)	Retrospective cohort study (hospitalization records)	652,979 GWVs (August 1990–July 1992) and 652,922 NDVs, stratified by California residence, service, and service branch of all 2,912,737 NDVs	Digestive system diseases	VA hospitals: PMR = 1.12 (95% CI 1.05–1.18); DoD hospitals: PMR = 0.98 (95% CI 0.96–0.99); COSHPD hospitals: PMR = 1.11 (95% CI 0.97–1.24)	Hospitalization records were matched on sex, age	Findings might be influenced by chance or by potential confounders, including health registry participation
Sosteck et al., 1996 (Vol. 8)	Cross-sectional, prevalence	57 male GWVs, 44 NDVs of National Guard unit	Questionnaire about GI and non-GI symptoms with recall before, during, and after Gulf War period	Prevalence of GI symptoms: abdominal pain 70% vs 9%; diarrhea 74% vs 18%; incomplete rectal evacuation 60% vs 7%; gas		Response rate 74%; Limited by small sample (recall before, during, after Gulf War),

Study	Study Design	Population	Outcomes	Results	Adjustments	Comments
				74% vs 23%; decreased appetite 42% vs 7% (all $p < 0.001$)		questionnaire (at time of assessment)
Gray et al., 2002 (Vol. 8)	Retrospective, case-control	U.S. Navy Seabees: 3,831 GWVs, 4,933 veterans deployed elsewhere, 3,104 NDVs	Self-reported physician diagnoses, self-reported symptoms from postal questionnaire	Gulf War Seabees vs NDVs: self-reported peptic ulcer disease (OR = 3.11, 95% CI 1.67–5.78); self-reported IBS (OR = 3.57, 95% CI 2.22–5.73); new GI disease diagnosed since September 1990 (OR = 2.10, 95 % CI 1.39–3.17); clustering of CFS, PTSD, MCS, IBS: Seabees who had one averaged 13–18 other symptoms; Seabees without one averaged only 6 other symptoms	Age, sex, active-duty or reserve status, race or ethnicity, current smoking, current alcohol drinking	Study limited by recall bias, IBS not analyzed exclusively, response rate 70%, large sample

NOTE: CFS = chronic fatigue syndrome; CI = confidence interval, COSHPD = California Office of Statewide Health Planning and Development; DoD = Department of Defense; GI = gastrointestinal; GWV = Gulf War veteran; NDV = nondeployed veteran; IBS = irritable bowel syndrome; MCS = multiple chemical sensitivity; OR = odds ratio; PMR = proportional morbidity ratio; PTSD = posttraumatic stress disorder; U.S. = United States.

CHRONIC SKIN CONDITIONS

Skin conditions are among the most frequent health problems reported by Gulf War veterans. Rash usually refers to *dermatitis*, an umbrella term covering several subtypes, including atopic dermatitis, contact dermatitis, seborrheic dermatitis, and psoriasis. All primary studies for chronic skin conditions are summarized in Table 4-17 at the end of this section.

Summary of Volumes 4 and 8

On the basis of two primary (Eisen et al., 2005; Higgins et al., 2002) and two secondary studies (Kang et al., 2000; Proctor et al., 1998) of dermatologic conditions, the Volume 4 committee determined that unrelated skin conditions occur more frequently among Gulf War deployed veterans compared with nondeployed veterans, but the findings were not consistent among studies. The Volume 4 committee noted that there is some evidence in deployed veterans of a higher prevalence of two distinct dermatologic conditions—atopic dermatitis and warts.

The Volume 8 committee identified an additional primary study (Ishoy et al., 1999b) that reported significantly greater rates of eczema; retarded wound healing; other skin problems; hair loss or hair disease; and sweaty, clammy, or damp hands in deployed Danish veterans than nondeployed veterans based on medical examination. However, there were no significant differences in the prevalence of psoriasis or nettle rash between deployed and nondeployed troops. Although the examination process used to verify the veteran's actual skin conditions at the time of the interview by the physician is somewhat unclear in the report, the use of a physician to discuss the veterans' responses to the questionnaire provided added validity to the study.

Secondary studies were largely consistent with the primary studies, but they lacked specificity regarding dermatologic outcomes or relied only on self-reported symptoms or self-reports of physician-diagnosed dermatologic conditions. Several large cohort studies reported similar findings in Gulf War veterans based on self-reported data collected by questionnaires. These results reflect higher rates of rash and skin irritation; dermatitis; and skin conditions other than dermatitis, skin cancer, eczema, or psoriasis among Gulf War veterans than control groups (Unwin et al., 1999; Proctor et al., 1998; Kelsall et al., 2004a). Additional secondary studies that relied on long lists of self-reported symptoms indicated that the prevalence of generally nonspecified skin conditions or conditions in deployed Gulf War veterans was greater than in nondeployed veterans including skin allergies or other skin conditions, sweating, itching skin, hair loss, boils, or abscesses; physician-diagnosed or treated skin conditions other than skin cancer; moderate or multiple skin symptoms; eczema; skin allergies; and dermatitis (Goss Gilroy Inc., 1988; Cherry et al., 2001a; Simmons et al., 2004; Steele, 2000, Wolfe et al., 1998; Proctor et al., 2001a; Gray et al., 1999a; Kang et al., 2000).

In summary, the Volume 8 committee found a high frequency of self-reports of various types of rash and other skin conditions among deployed versus nondeployed veterans, and, in general, these reports were confirmed by dermatologic examination. Overall, very few studies rigorously assessed the prevalence of skin conditions in Gulf War veterans, and results are mixed, with increases for some skin conditions but not for others. Furthermore, there was no consistency across these studies, which suggests that the findings could have occurred by chance. Finally, most of the studies are weak in design and limited by self-selection and possible

reporting bias. *The Volume 8 committee concluded that there was insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and skin disorders.*

New Literature

New literature pertaining to skin conditions in Gulf War veterans includes two secondary studies, and one other related study. The committee did not identify any new primary studies.

Secondary Study

Sim et al. (2015) conducted the Australian Gulf War Veterans' Follow Up Health Study between 2011 and 2013 to assess the entire Australian Gulf War cohort 10 years after the 2000–2002 baseline study and 20 years after the war. Results were adjusted for age, rank category, and service branch, but not for smoking. Of the 1,456 eligible deployed veterans, 715 participated in the study and 675 of the 1,449 nondeployed veterans made up the comparison group. Skin conditions were based on self-reports and on self-reports of doctor diagnoses. Statistically significantly more deployed veterans reported having dermatitis (RR = 2.21, 95% CI 1.35–3.59) and eczema (RR = 2.84, 95% CI 1.43–5.65) than nondeployed veterans. There was no significant difference in reporting of doctor-diagnosed psoriasis (RR = 1.11, 95% CI 0.66–1.85).

Dursa et al. (2016) published on the most recent results of the third survey wave of the cross-sectional National Health Study of Persian Gulf War Era Veterans. The wave 3 survey (discussed in greater detail in Chapter 3), conducted in 2012–2013, asked 8,104 deployed and 6,148 Gulf War era veterans to indicate whether a doctor had ever told them they had dermatitis. The weighted prevalence was 27.4% and 21.1% in the deployed and era veterans, respectively, and the odds of dermatitis were statistically significantly increased in the deployed compared with the era veterans (OR = 1.44, 95% CI 1.27–1.63).

Other Related Studies

VA provided a health care use report for Gulf War deployed and era veterans who sought care in VA facilities from October 2001 to December 2013. The report presented the prevalence of diagnoses of diseases by ICD-9 code categories, including diseases of skin (ICD-9 categories 680–709) (Table 4-18). 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. A total of 286,995 Gulf War deployed and 296,635 era veterans received treatment at VA over the approximately 11-year period (VA, 2014a,b). These VA health care users represent 46% of all deployed Gulf War veterans and 36% of all nondeployed era veterans.

Conclusions

Both the Volume 4 and Volume 8 committees noted a high frequency of self-reports of various types of skin conditions among deployed versus nondeployed veterans, but the specific skin conditions found were not consistent across the studies. For the most part, the studies, while occasionally using a dermatologic examination to confirm the skin conditions, did not include adequate assessment of the skin conditions. In Volume 10, the one new secondary study further suggested that while self-reports of some skin conditions such as dermatitis and eczema are more prevalent in deployed Gulf War veterans, others such as psoriasis are not. The committee finds

TABLE 4-18 Ten Most Frequent Diagnosed Skin Diseases for Deployed and Nondeployed Gulf War Veterans Seeking Health Care in VA Between 2002 and 2013

Diagnosis	Deployed N = 88,012 (%)	Nondeployed N = 80,617 (%)
Contact dermatitis, other eczema	31.8	29.7
Other disorders of skin, subcutaneous tissue	21.4	22.0
Diseases of sebaceous glands	20.7	20.9
Other cellulitis, abscess	19.0	18.5
Other dermatoses	14.4	17.9
Other hypertropic, atrophic conditions of skin	12.7	13.7
Diseases of hair, hair follicles	11.5	10.6
Diseases of nails	9.5	10.8
Pruritus, related conditions	7.5	7.5
Corns and callosities	7.4	8.5

SOURCE: VA (2014a,b).

that given the aging of the population of Gulf War veterans and the unlikelihood that new chronic skin conditions will develop 25 years after the Gulf war that are attributable to their Gulf War service, it is doubtful that further assessments will show increased risk of these conditions.

Therefore, the Volume 10 committee concludes that there is insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and skin conditions.

TABLE 4-17 Chronic Skin Conditions

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Eisen et al., 2005 (Vol. 4)	Population-based, cross-sectional, prevalence, medical evaluation	1,061 U.S. GWVs and 1,128 NDVs	Atopic dermatitis and verruca vulgaris (warts)	Atopic dermatitis: 1.2% vs 0.3% (OR = 8.1, 95% CI 2.4–27.7); verruca vulgaris (warts): 1.6% vs 0.6% (OR = 4.02, 95% CI 1.28–12.6)	Age, sex, race, years of education, smoking, duty type, service branch, rank	Low participation rates, especially among nondeployed
Higgins et al., 2002 (Vol. 4)	Prospective case-comparison study	111 disabled and 98 nondisabled UK GWVs; 133 disabled NDV controls (54 deployed to Bosnia and 79 nondeployed era controls) (population randomly sampled from Ismail et al., 2002, cohort)	Skin conditions	No significant difference in prevalence of all skin conditions combined: Disabled GWVs: 47.7% Nondisabled GWVs: 36.7% Disabled NDVs: 42.8% Sebhorrheic dermatitis: 8.1% in disabled deployed vs 2.3% in disabled nondeployed ($p = 0.06$)	Age, sex, rank, smoking, and alcohol	Response rates: Disabled GWVs: 67% Nondisabled GWVs: 62% Disabled Bosnia: 55% Disabled NDVs: 43%
Ishoy et al., 1999b (Vol. 8)	Cross-sectional, prevalence	686 Danish GWV peacekeepers deployed to gulf in 1990–1997 vs 231 age- and sex-matched NDVs	Health examination by physician, self-report questionnaire	Prevalence of skin conditions with onset after gulf: eczema 15.0% vs 3.0%, $p < 0.001$; retarded wound healing 6.0% vs 1.7%, $p < 0.01$; other forms of skin problems 17.1% vs 5.2%, $p < 0.001$; hair loss or hair disease 4.2% vs 0.9%, $p < 0.01$; sweaty, clammy, or damp hands 7.9% vs 3.9%, $p < 0.05$	Lack of information on adjustment for confounders in multivariate analysis	Participation rate 83.6% deployed, 57.8% nondeployed

NOTE: CI = confidence interval; GWV = Gulf War veteran; NDV = nondeployed veteran; OR = odds ratio; UK = United Kingdom; U.S. = United States.

PAIN-RELATED CONDITIONS

This section discusses health conditions that are hard to diagnose and that are typically manifest with multiple symptoms including chronic fatigue, headaches, and muscle and joint pain. These conditions are also associated with impairment of function and increased use of health care. Diagnostic criteria for CFS, fibromyalgia, and rheumatic disorders such as rheumatoid arthritis and osteoarthritis are distinct, but the conditions have overlapping symptoms and in some cases may be difficult to distinguish from each other and from related conditions such as chronic widespread pain (CWP) and Gulf War illness, that are seen in many Gulf War veterans.

In 2010, the American College of Rheumatology (ACR) published new diagnostic criteria for fibromyalgia that updated the 1990 criteria to revise the distribution and intensity of symptoms as essential elements of the diagnosis. The new criteria removed the requirement for a clinician rating and rely solely on subjective information from the patient. The result may be that more people will be diagnosed with fibromyalgia. The new criteria may also shift the demographic profile of people with fibromyalgia to include more men (Bennet et al., 2014), which would significantly affect the rate of fibromyalgia observed in a population of mostly men, such as Gulf War veterans. While all the studies in this report that assessed fibromyalgia used the 1990 criteria, new studies may show different trends or associations based on the new criteria. Additionally, exclusive reliance on self-report in the most recently revised criteria for fibromyalgia contrasts with the importance that this committee assigned to studies based on objective outcomes. It will be important to consider the two sets of criteria if the prevalence of fibromyalgia using the new criteria is compared with studies using the old criteria.

CFS, also known as myalgic encephalomyelitis, was recently assessed by another IOM committee (IOM, 2015). That committee proposed new diagnostic criteria and a new name for the condition, systemic exertion intolerance disease (SEID). The new criteria were based on a systematic review of the evidence. It is not clear what effect the new definition will have on future epidemiologic studies; the studies reviewed in this chapter did not adopt the new name nor use the new diagnostic criteria. In Volumes 4 and 8, pain-related conditions were considered as separate entities as there was considerable literature on each in Gulf War veterans. However, for this volume, there is little new scientific information on the prevalence of these conditions in Gulf War veterans. Many of the studies look at more than one condition. Therefore, this committee has chosen to assess the literature on these conditions in one section to highlight the differences and overlap in the new data. All primary studies of pain-related conditions are summarized in Table 4-19 at the end of this section.

Summary of Volumes 4 and 8

In Volume 4, CFS and fibromyalgia were considered in separate sections as were conditions of the musculoskeletal system such as arthritis and arthralgia. Chronic pain was considered in the section on symptoms, signs, and abnormal laboratory findings (ICD-10 R00–R99). In volume 8, CFS was discussed in the section on multisymptom illnesses and there were separate sections on fibromyalgia and CWP, and on musculoskeletal conditions.

Chronic Fatigue Syndrome

The CDC case definition for CFS requires fatigue and related impairment in function, and the occurrence of four of eight other defining symptoms for at least 6 months (Fukuda et al., 1994). Of the eight symptoms, the most commonly reported are headaches, postexertional malaise, impaired cognition, and muscle pain (Buchwald and Garrity, 1994). This definition is widely used by researchers, although some studies describe a "CFS-like" syndrome. The Volume 4 and Volume 8 committees considered a primary study for CFS to be one in which CFS had been diagnosed according to the CDC criteria and a secondary study to be one in which a CFS-like condition was documented. Self-reports of CFS or self-reports of a physician's diagnosis of CFS were not included among the primary studies because such self-reports are frequently inaccurate. Neither committee included studies that lacked a control group; estimated the prevalence of symptoms of "chronic fatigue" or multisymptom illness; or used scalar measures of disability and poor quality of life related to health as surrogates for the CDC criteria.

The Volume 4 committee reviewed one primary and four secondary studies and noted that because the diagnosis of CFS depends entirely on symptoms, not on physical or laboratory findings, the prevalence was variable from study to study. The one primary study (Eisen et al., 2005) demonstrated a higher prevalence of CFS in deployed versus nondeployed veterans (1.6% vs 0.1%; OR = 40.6, 95% CI 10.2–161.15). All the secondary studies (Goss Gilroy Inc. 1998; Iowa Persian Gulf Study Group, 1997; Kang et al., 2003; Proctor et al., 2001b) also showed a higher prevalence of CFS or CFS-like illnesses among veterans deployed to the Persian Gulf than among their nondeployed or deployed elsewhere counterparts.

The Volume 8 committee identified two new primary studies (Ismail et al., 2008; Kelsall et al., 2006) and one new secondary study (Lucas et al., 2007). One study in Australian Gulf War veterans showed that CFS and complaints of unexplained chronic fatigue were increased in deployed versus nondeployed veterans (CFS OR = 1.2, 95% CI 0.5–2.9; chronic fatigue lasting more than 6 months OR = 1.9, 95% CI 1.4–2.7) (Kelsall et al., 2006). CFS was also more prevalent in disabled Gulf War veterans from the UK compared with either nondeployed or deployed elsewhere veterans who had similar levels of disability (OR 7.8, 95% CI 2.5–24.5) (Ismail et al., 2008).

CFS and complaints of unexplained chronic fatigue appear to be increased in deployed Gulf War veterans compared to contemporaneous cohorts (either nondeployed or deployed elsewhere). Those results were also observed in several cross-sectional population-based studies that used self-reports to define CFS or chronic fatigue. However, the absolute prevalence of these symptoms varied considerably from study to study. Associations between fatigue, subjective neurological symptoms, and exposures were also based entirely on retrospective self-reports. *Therefore, the Volume 8 committee concluded that there was sufficient evidence for an association between deployment to the Gulf War and chronic fatigue syndrome.*

Fibromyalgia and Chronic Widespread Pain

Fibromyalgia is characterized by widespread muscle and skeletal pain in combination with point tenderness at numerous soft tissue sites. Although a diagnosis of fibromyalgia cannot be confirmed through pathologic or laboratory tests, the ACR established diagnostic criteria for clinical examinations (Wolfe et al., 1990).[12] The case definition requires both widespread pain

[12] In 2013, the ACR revised the criteria for fibromyalgia. However, no studies reviewed in this section use the revised criteria.

(pain on both sides of the body, above and below the waist, and including axial skeletal pain) lasting for at least 3 months and pain (not just tenderness) in at least 11 of 18 tender point sites on palpation with an approximate force of 4 kg. Other symptoms of fibromyalgia include fatigue, sleep disturbance, morning stiffness, and cognitive impairment, but those are not sensitive and specific enough to use for classification; fibromyalgia may be considered to be a subset of CWP (Wolfe et al., 1990). The disorder is chronic and varies in intensity (Wolfe et al., 1997). It has been estimated that the prevalence of fibromyalgia in the general U.S. population is about 3% in women and about 0.5% in men, and its prevalence increases with age (Wolfe et al., 1995).

Among the pain-related disorders, studies reviewed by the current and past Gulf War and Health committees, none of the studies have used the recently changed diagnostic criteria of fibromyalgia that base diagnosis on self-report (Bennett, 2014). These new criteria would likely have the effect of changing the inclusion criteria for fibromyalgia. This change in diagnostic criteria may also increase the diagnosis in males and therefore may increase the proportion of Gulf War veterans meeting criteria for fibromyalgia. Despite the recent change in the diagnostic criteria for fibromyalgia, the complete reliance on self-report may change the results and interpretive value of investigative studies, thus future researchers will have to weigh this in their planning.

The ACR defines CWP as "the presence of pain above and below the waist, or on both the left and right sides of the body, for 3 months or longer." Prior studies have reported CWP prevalence rates between 11% and 13% in Germany, Sweden, the United Kingdom, and the United States. Several studies have reviewed the presence of chronic pain in Gulf War veterans, but its definition varies by study. Many studies of Gulf War veterans reported increased pain symptoms that could be clustered into CWP, but the terminology used in the studies is not consistent and includes joint pain and general aches and pain; these pain clusters may or may not meet the ACR criteria for CWP. The committee required that primary studies include a physical examination and not rely solely on symptom reporting by patients.

In Volume 4, only one study used the full ACR case definition of fibromyalgia (Eisen et al., 2005), including criteria based on physical examination and found significantly more deployed Gulf War veterans than nondeployed veterans diagnosed with fibromyalgia (OR = 2.32, 95% CI 1.02–5.27). However, another study based on hospitalizations for fibromyalgia assessment found no association between Gulf War deployment and hospitalization for fibromyalgia in active-duty service members. These findings are consistent with other study findings since few cases of fibromyalgia are severe enough to warrant hospitalization. In two large, but secondary, cohort studies, deployed veterans reported significantly increased fibromyalgia symptoms compared with nondeployed veterans but those findings are of limited value as the studies did not include physical examinations. The Volume 4 committee concluded that there was a higher prevalence of fibromyalgia among deployed than nondeployed Gulf War veterans.

The Volume 8 committee reviewed one primary study (Ang et al., 2006) and three secondary studies on Gulf War deployment and CWP. Although each of the studies found a higher prevalence of CWP in deployed than in nondeployed veterans, all of them had considerable limitations. The primary study that looked specifically at CWP was a large random sample of veterans who reported significantly more bodily pain than did nondeployed veterans; a 10-year follow-up study of a subset of these veterans who had not met the classification criteria for CWP at 5 years after the war, found that the prevalence of CWP at 10 years after the war had increased both with combat exposure and with perception of life stress at the time of deployment.

Three secondary studies indicated that pain symptoms were reported more frequently in deployed than nondeployed veterans. *The Volume 8 committee concluded that there was limited but suggestive evidence of an association between deployment to the Gulf War and both fibromyalgia and chronic widespread pain.*

Conditions of the Musculoskeletal System

Arthritis is the most common form of joint disease and is generally related to major trauma, repetitive joint use, heavy manual material handling, and age. Arthralgia, which is a self-reported symptom of arthritis, refers to painful joints. In the absence of other clinical features and radiographic findings, arthralgias are not necessarily diagnostic of arthritis.

The Volume 4 committee found that in the one primary and two secondary studies that examined these outcomes, there was no statistically significant difference in arthralgias for the deployed versus nondeployed Gulf War veterans who underwent a medical examination. The primary study by Eisen et al. (2005) found a nonsignificant increased risk arthralgias in deployed veterans (OR = 1.5, 95% CI 0.70–1.89). The secondary studies also indicated that self-reports of arthritis was more common among those deployed to the gulf.

The Volume 8 committee identified five new primary studies that looked at hospitalization discharge diagnoses of some form of musculoskeletal disease in Gulf War veterans, but specific diagnoses were not provided in any of the studies. Those studies showed no increased risk of hospitalization for musculoskeletal system conditions among Gulf War deployed veterans compared with their nondeployed counterparts. Possible exposure to smoke from oil-well fires and nerve agents from the Khamisiyah demolition also failed to result in increased hospitalizations. The committee notes, however, that many musculoskeletal conditions, such as arthritis, do not typically require hospitalization and are more likely to be treated on an outpatient basis. *The Volume 8 committee concluded that there was insufficient/inadequate evidence to determine whether an association exists between deployment to the Gulf War and musculoskeletal system conditions.*

New Literature

The committee did not identify any new primary studies for any pain-related disorders in Gulf War veterans. The committee did review four studies that met its criteria for a secondary study (Dursa et al., 2016; Kelsall et al., 2014; Li et al., 2011a; Sim et al., 2015).

Secondary Studies

Li et al. (2011a) conducted a 10-year follow-up survey of 5, 469 U.S. Gulf War deployed and 3,353 nondeployed veterans who had also participated in the 1995 VA National Health Survey. Compared with nondeployed veterans, the authors found that in 2005 deployed veterans were no more likely to report the persistence of the most prevalent chronic conditions in the past year including arthritis (RR = 1.10, 95% CI 0.93–1.10) and CFS-like illness (RR = 1.63, 95% CI 0.72–3.72) than nondeployed veterans. However, deployed veterans had a statistically significant increased risk of reporting a new onset of both arthritis (RR = 1.24, 95% CI 1.11–1.39) and CFS-like illness (RR = 2.36, 95% CI 1.90–2.93) since 2005 than nondeployed veterans. The risk ratios were adjusted for age in 2005, gender, race, rank, service branch, service type, BMI, and current cigarette smoking.

In a cross-sectional study, Kelsall et al. (2014) compared 1,381 Australian veterans of the Gulf War with 1,377 veterans who were serving in the military at the time or had previously

deployed. The assessment, conducted in 2000–2002, queried veterans about doctor-diagnosed arthritis or rheumatism, back or neck problems, joint problems, and soft tissue disorders. Medical practitioners then rated the self-reported diagnoses as nonmedical, unlikely, possible, or probable; only probable diagnoses were analyzed. This approach, which added a level of medical judgment to the self-reported conditions but did not verify the self-reported diagnoses with a clinical evaluation, showed that the odds of having any musculoskeletal disorder was increased for the deployed veterans (OR = 1.19, 95% CI 1.00–1.43), but the odds of having any specific disorder was not. Depression was significantly associated with having any musculoskeletal disorder (OR = 1.81, 95% CI 1.21–2.69), arthritis or rheumatism (OR = 3.42, 95% CI 1.64–7.14), and back or neck problems (OR = 2.32, 95% CI 1.49–3.60), but not joint problems (OR = 1.51, 95% CI 0.88–2.58) in deployed veterans. However, depression was also significantly associated with the same disorders, including joint problems, in the comparison group. PTSD was significantly associated with arthritis or rheumatism (OR = 2.89, 95% 1.21–6.86) and joint problems (OR = 1.97, 95% CI 1.05–3.70) in the deployed veterans and significantly associated with all the musculoskeletal disorders except arthritis or rheumatism in the comparison group.

Sim et al. (2015) reported on the Australian Gulf War Veterans' Follow Up Health Study, conducted between 2011 and 2013 (this study was a follow-up to the baseline study discussed in Volume 8). This study is an assessment of the entire 1,871 Australian Gulf War cohort 10 years after the 2000–2002 baseline study and 20 years after the war. Because only about 2% of the participants were women, only males were recruited for the study. Results were adjusted for age, rank category, and service branch. Of the 1,456 eligible deployed veterans, 715 participated in the study and 675 of the 1,449 nondeployed veterans provided the comparison group. Fatigue and musculoskeletal symptoms were based on responses to questions about the veterans' experience with fatigue, prolonged fatigue (at least 1 month duration), and chronic fatigue (at least 6 months duration). Deployed veterans (n = 697) were significantly more likely than nondeployed veterans (n = 659) to report extreme tiredness or fatigue (RR = 1.38, 95% CI 1.15–1.65), prolonged fatigue (RR = 1.37, 95% CI 1.04–1.80), or chronic fatigue (RR = 1.41, 95% CI 1.02–1.96). The Chalder Fatigue Scale[13] was used to assess fatigue severity, and results indicated that deployed veterans met the standardized diagnostic criteria more frequently than nondeployed veterans (RR = 1.23, 95% CI 1.04–1.45). Furthermore, the prevalence of prolonged fatigue and chronic fatigue more than doubled from baseline to follow-up in both the deployed and nondeployed groups, and these increases were statistically significant.

Veterans were also categorized into one of five chronic pain grades. Although deployed veterans were more likely to report both greater intensity pain and more disability from it than nondeployed veterans, the differences were not statistically significant. Compared with nondeployed veterans, deployed veterans had pain in more body areas in the previous 7 days (based on categories of four to six body areas, OR = 1.47, 95% CI 1.12–1.93, and 11 or more body areas of pain, OR = 2.89, 95% CI 1.01–8.28, but not in 7 to 10 body areas). Gulf War veterans also report more pain-related health symptoms in the past month, general muscle aches or pains, headaches, and low back pain. More than half of both deployed and nondeployed veterans reported those symptoms. Finally, with regard to musculoskeletal disorders, the follow-up study asked more specific questions than the baseline study, so longitudinal comparisons were not made. In the follow-up study, veterans were asked whether they had a doctor diagnosis of or had been treated for osteoarthritis, rheumatoid arthritis, other inflammatory arthritis, or gout

[13] The Chalder fatigue scale is widely used to measure physical and mental fatigue in CFS patients (Chalder et al., 1993).

since 2001. There were no statistically significant differences between the deployed and nondeployed groups for any of the musculoskeletal disorders; osteoarthritis was the most common ailment in both groups (Sim et al., 2015).

The third wave of the VA's National Health Study of Persian Gulf War Era Veterans conducted about 20 years after the war, asked 8,104 deployed and 6,148 Gulf War era veterans to indicate whether a doctor had ever told them they had a medical condition and then whether the condition had been present in the previous 4 weeks. Dursa et al. (2016) found a statistically significant difference between the deployed and era veterans in the prevalence of self-reported CFS (11.8% vs 5.3%; OR = 2.36, 95% CI 1.94–2.86), fibromyalgia (3.7% vs 2.9%; OR = 1.48, 95% CI 1.15–1.91), rheumatoid arthritis (9.9% vs 7.9%; OR = 1.40, 95% CI 1.17–1.67), and arthritis not specified (33.9% vs 31.8%; OR = 1.16, 95% CI 1.05–1.29). Self-reported osteoarthritis was not statistically significantly different between deployed and era veterans (OR = 1.06, 95% CI 0.92–1.23). The ORs were adjusted for age, race, sex, BMI, smoking status, service branch, and unit component.

Other Related Studies

VA provided a health care use report for Gulf War deployed and era veterans who sought care in VA facilities from October 2001 to December 2013. The report presented the prevalence of diagnoses of diseases by ICD-9 code categories, including diseases of the musculoskeletal systems and connective tissue (ICD-9 categories 710–739) (Table 4-20). 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. A total of 286,995 Gulf War deployed and 296,635 era veterans received treatment at VA over the approximately 11-year period (VA 2014a,b). These VA health care users represent 46% of all deployed Gulf War veterans and 36% of all nondeployed era veterans.

TABLE 4-20 Ten Most Frequent Diagnosed Diseases of the Musculoskeletal System and Connective Tissue for Deployed and Nondeployed Gulf War Veterans Seeking Health Care in VA Between 2002 and 2013

Diagnosis	Deployed N = 182,473 (%)	Nondeployed N = 168,543 (%)
Other, unspecified disorders of joint	65.4	64.2
Other, unspecified disorders of back	55.8	56.0
Osteoarthrosis, allied disorders	38.0	39.5
Other disorders of soft tissues	27.7	27.3
Peripheral enthesopathies, allied syndromes	22.8	23.6
Other disorders of cervical region	20.4	21.4
Intervertebral disc disorders	17.3	18.2
Disorders of muscle, ligament, fascia	14.4	15.1
Other and unspecified arthropathies	13.4	13.5
Other disorders of synovium, tendon, bursa	11.7	12.6

SOURCE: VA (2014a,b).

Other studies have assessed the effect of a co-occurring health disorder (e.g., musculoskeletal disorders) on the prevalence of PTSD. Using data from the Patient Health Questionnaire component of the second wave of the VA National Health Survey of Gulf War Era Veterans, Coughlin and colleagues (2011a) found that among 6,111 Gulf War deployed and 3,859 era veterans, CFS, fibromyalgia, or arthritis was more commonly reported by obese veterans compared with normal weight veterans. This was also true for having a CFS-like illness in the past 12 months for obese nondeployed veterans but not for obese deployed veterans. Further assessment of these veterans found that having a self-reported CFS-like illness was also more prevalent among deployed and era Gulf War veterans with problem drinking than those without problem drinking. Gulf war veterans, deployed or era, were at significantly increased risk of having a CFS-like illness if they had problem drinking (OR = 1.48, 95% CI 1.22–1.78, adjusted for age, sex, race/ethnicity, branch of service, rank, and deployment status) (Coughlin et al., 2011b). Heavy drinking was defined as ≥ 15 drinks per week.

Individuals with fibromyalgia typically experience an exacerbation of their symptoms following acute exercise. In an effort to determine whether Gulf War veterans with chronic widespread pain had a similar reaction to exercise, Cook et al. (2010) assessed 27 Gulf war veterans from a VA medical center, 11 of whom had chronic muscle pain and 16 healthy controls. There was no difference between the two groups with regard to heat and pressure pain thresholds either before or after exercise; however, after exercise (submaximal cycling) veterans with chronic muscle pain rated the heat-pain stimuli after exercise as more intense and reported greater leg-muscle pain intensity during exercise compared with the healthy controls.

Two studies tested for differences in synovial fluid in veterans with Gulf War illness complaining of joint pain compared to patients with either osteoarthritis or rheumatoid arthritis (Diaz-Torne et al., 2007; Pessler et al., 2008). Neither found evidence of synovitis in veterans with Gulf War illness using tests that easily detected synovitis in the arthritis patients.

Conclusions

There were no new studies that were of sufficient quality to be considered primary studies for Volume 10. Four secondary studies described inconsistent results for pain-related disorders among deployed veterans.

CFS was assessed in two new secondary studies that reported increased CFS (Dursa et al., 2016) and new onset CFS (Li et al., 2011a). Sim et al. (2015) found increased chronic fatigue and greater severity of it in deployed veterans. These results lend further support to the conclusion reached by the Volume 8 committee. Furthermore, the Volume 10 committee believes that the changes to the CFS case definition discussed at the beginning of this section will not significantly affect its conclusions with regard to the association between CFS and deployment to the Gulf War.

Reports for fibromyalgia and chronic pain are described in two studies. Sim et al. (2015) found that deployed veterans reported greater pain intensity and more disability than nondeployed veterans, but the differences were not statistically significant; however, deployed veterans reported statistically significantly more pain in more body areas, and Dursa et al. (2016) reported a statistically significant greater rate of fibromyalgia in deployed veterans compared with era veterans. While these results are suggestive of an association between chronic pain and fibromyalgia and deployment, their reliance on self-reports limits the committee's confidence in the association.

Evidence for musculoskeletal disorders was less consistent in the three studies that reported this outcome, which supports the Volume 8 conclusion of insufficient/inadequate evidence. Sim et al. (2015) found no statistically significant differences between the deployed and nondeployed groups for any of the musculoskeletal disorders, but deployed veterans reported more general muscle aches or pains and low back pain. Li et al. (2011a) found that rates of arthritis were similar in both groups, but deployed veterans were more likely to report new onset arthritis. Kelsall et al. (2014) found increased rates of any self-reported musculoskeletal disorder in deployed veterans but not for specific conditions, such as arthritis. Despite the limited number of musculoskeletal disorders studies in this cohort, the aging Gulf War veteran cohort is likely to experience an increase in musculoskeletal disorders studies over time, consistent with the prevalence of musculoskeletal disorders documented in other occupational groups and the general population.

Thus, the committee finds that given the effects of aging and the unlikelihood that new pain-related conditions that are attributable to service in the Gulf War will develop 25 years later, it is doubtful that further assessments will show an increased risk of these conditions. Should these conditions be followed in this cohort, differences in musculoskeletal disorders by gender and race/ethnicity should be reported when data are available.

Therefore, the Volume 10 committee concludes that that there is sufficient evidence for an association between deployment to the Gulf War and chronic fatigue syndrome; that there is limited/suggestive evidence of an association between deployment and both fibromyalgia and chronic widespread pain; and that there is insufficient/inadequate evidence to determine whether an association exists between deployment and musculoskeletal system conditions.

Table 4-19 Pain-Related Conditions

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Chronic Fatigue Syndrome						
Eisen et al., 2005 (Vol. 4)	Population-based, cross-sectional, prevalence, in-person medical and psychiatric evaluations	1,061 GWVs vs 1,128 NDVs; selected from among those who had participated in 1995 National Health Survey of Gulf War Era Veterans and Their Families (mail and telephone survey) (Kang et al., 2000)	CFS based on in-person interviews according to CDC CFS criteria and exclusionary diagnoses from history, interviews, examinations, laboratory testing	OR = 40.6 (95% CI 10.2–161.2)	Age, sex, race, smoking, duty type, service branch, rank	Low participation rates (53% of GWVs and 39% of NDVs), but analysis of nonparticipants and participants reveals that participants, both GWVs and NDVs, are more likely to report symptoms of CFS
Kelsall et al., 2006 (Vol. 8)	Cross-sectional survey	1,424 Australian male GWVs, 1,548 male NDVs frequency matched by age and service type (Same population as Kelsall et al., 2004a,b, 2005)	Association of unexplained chronic fatigue and CFS determined in clinical assessment with self-reported exposure to various stressors	CFS in deployed veterans vs control groups OR = 1.2 (95% CI 0.5–2.9) Chronic fatigue (≥ 6 months) OR = 1.9 (95% CI 1.4–2.7) 91 (6.6%) GWVs had unexplained chronic fatigue vs 40 (2.9%) of controls (OR = 2.3, 95% CI 1.6–3.4) Unexplained chronic fatigue in GWVs associated with PB (OR = 2.8, 95% CI 1.3–6.1), oil-well fire smoke (OR = 2.0, 95% CI 1.2–3.4), pesticides (OR = 2.4, 95% CI 1.5–3.8), presence in chemical weapons area (OR = 4.6, 95% CI 2.7–7.8), and deployed during air	Age, service branch, rank; also education, marital status, smoking, and alcohol use for unexplained chronic fatigue.	Relatively large study with national ascertainment; response rate 80.5% for deployed, 56.8% for nondeployed Exposures self-reported; possible recall bias

Study	Design	Population	Outcomes	Results	Adjustments	Comments
				war (OR = 2.3, 95% CI 1.1–4.5)		
Ismail et al., 2008 (Vol. 8)	Two-phase cohort study; first phase population-based postal survey, second phase random sample of disabled phase 2 responders	111 deployed GWVs; 133 era veterans, including Bosnia peacekeepers; must have physical disability (less than 72.2 on SF-36 physical functioning scale from phase 1 survey) (Population derived from Unwin et al., 1999, and Ismail et al., 2002)	CFS determined through clinical assessment using CDC criteria	20 disabled GWVs (18%) and 4 disabled controls (3%), OR = 7.8, 95% CI 2.5–24.5	Age, sex, rank, marital status, alcohol-disorders, selection bias via probability weights	Phase 1 response rate 70% for GWVs, 60% and 63% for Bosnia and era veterans, respectively. Phase 2 response rate 67% for GWVs, 55% and 43% for Bosnia and era veterans, respectively. 54% of GWVs with CFS had concomitant depression or anxiety disorder
Fibromyalgia and Chronic Widespread Pain						
Eisen et al., 2005 (Vol. 4)	Population-based, cross-sectional, prevalence, medical evaluation	1,061 U.S. GWVs, 1128 NDVs	Symptoms and physical examination using criteria of American College of Rheumatology	Prevalence: 2.0% vs 1.2%, OR = 2.32 (95% CI 1.02–5.27)	Age, sex, race, years of education, cigarette smoking, duty type, service branch, rank	Uses gold standard for diagnosis of fibromyalgia; low participation rates, especially among nondeployed
Smith et al., 2000 (Vol. 4)	Postwar hospitalization study	551,841 GWVs, 1,478,704 NDVs	Hospitalization (1991–1997); Cox proportional-hazards models ICD-9 codes for fibromyalgia	RR = 1.23 (95% CI 1.05–1.43); however, survival curves indicate excess due to hospitalization only for purposes of evaluation	Sex, age, branch of service	No increase after accounting for CCEP effect; limited to active duty; most cases of fibromyalgia are not severe enough to warrant

Study	Design	Population	Outcomes	Results	Adjustments	Comments
			(729.1)	during the CCEP; before CCEP: RR = 0.92 (95% CI 0.74–1.13)		hospitalization
Ang et al., 2006 (Vol. 8)	Cohort of veterans from IPGWSG	370 veterans who were free of CWP at 5 years were examined 10 years after war: 267 GWVs, 103 NDVs	Structured telephone interview about 5 years after the war; in-person follow-up medical examination 10 years after war of 370 veterans who did not report chronic widespread pain 5 years after war	Neither deployment to nor time in gulf region significantly correlated with CWP: OR = 1.1, 95% CI 0.6–2.0 and OR = 1.0, 95% CI 0.7–13.0, respectively; combat exposure correlated: OR = 1.5, 95% CI 1.1–2.0; perception of stress due to military experience at time of war correlated more significantly with CWP: OR = 1.6, 95% CI 1.1–2.3, $p = 0.0084$	Controls matched for age, sex, branch of service	Potential for recall bias; only veterans who were free of CWP at 5 years were assessed 10 years after war
Conditions of the Musculoskeletal System						
Eisen et al., 2005 (Vol. 4)	Population-based, cross-sectional, prevalence, medical evaluation	1,061 U.S. GWVs vs 1,128 NDVs	Persistent and clinically significant bone or joint symptoms with or without joint effusion, and treatment with anti-inflammatory agents, narcotic pain medications,	Prevalence: 6.4% vs 6.8% (OR = 1.15, 95% CI 0.70–1.89)	Age, sex, race, years of education, smoking, duty type, service branch, rank	Low participation rates, especially among nondeployed

Study	Design	Population	Outcomes	Results	Adjustments	Comments
			or nonnarcotic pain medications			
Gray et al., 1996 (Vol. 8)	Retrospective cohort, hospitalizations from August 1991 through September 1993	547,076 active-duty GWVs, 618,335 NDVs	Hospital-discharge diagnoses of musculoskeletal system diseases in DoD hospital system	Exact values not given 1991: OR < 1.0 (95% CI < 1.0); 1992: OR < 1.0 (95% CI < 1.0) 1993, OR about 1.01 (95% CI 0.9–1.15)	Prewar hospitaliz-ation, sex, age, race, service branch, marital status, rank, length of service, salary, occupation	Short follow-up period; no outpatient data; restriction to DoD hospitals, and thus to persons remaining on active duty after the war; no adjustment for other potential confounders
Gray et al., 2000, (Vol. 8)	Retrospective cohort, hospitalizations from August 1991 through December 1994	652,979 GWVs, 652,922 randomly selected NDVs 182,164 DoD hospitalizations; 16,030 VA hospitalizations; 5,185 COSHPD hospitalizations	Hospital-discharge diagnoses of musculoskeletal system diseases in DoD, VA, and COSHPD hospital systems	DoD PMR = 1.01 (95% CI 0.99–1.02) VA PMR = 0.86 (95% CI 0.81–0.91) COSHPD PMR = 0.79 (95% CI 0.64–0.93)	Age, sex, race (only for DoD PMR)	Able to assess only illnesses that resulted in hospitalization; possible undetected confounders PMR has lower sensitivity than a comparison of hospitalization rates
Smith et al., 2006 (Vol. 8)	Retrospective cohort study (cohort data from DMDC)	Active-duty personnel with a single deployment to: Gulf War theater (n = 455,465); southwest Asia peacekeeping mission, 1991–1998 (n = 249,047); Bosnia, 1995–1998 (n =	Postdeployment hospitalization events (1991–2000) for an ICD-9-CM diagnosis of a musculoskeletal system disease (ICD-9 codes 710–739)	Compared to GWVs, veterans of Bosnia showed reduced risk (HR = 0.78, 95% CI 0.71–0.86), veterans of southwest Asia at slightly increased risk (HR = 1.06, 95% CI 1.01–1.12)	Sex, age, marital status, pay grade, race/ethnicity, service branch, occupation, and pre-deployment hospitaliz-ation; time-dependent	Limitations: active-duty personnel only; hospitalizations at DoD facilities only

Study	Design	Population	Outcomes	Results	Adjustments	Comments
		44,341)			covariate to account for changing hospitalization methods, diagnostic criteria, and procedures	
Smith et al., 2002 (Vol. 8)	DoD hospitalizations 1991–1999; exposure modeling for oil-well fire smoke	405,142 active-duty GWVs who were in theater during the time of Kuwaiti oil-well fires	Hospitalization for musculoskeletal system diseases (ICD-9-CM codes 710–739)	No association between exposure and musculoskeletal system diseases across all exposure levels	Adjusted for "influential covariates," defined as demographic or deployment variables with *p* values less than 0.15	Objective measure of disease not subject to recall bias; no issues with self-selection; however, only DoD hospitals, only active duty, no adjustment for potential confounders such as smoking
Gray et al., 1999b (Vol. 4)	DoD hospitalizations 1991–1995, exposure to nerve agents at Khamisiyah based on 1997 DoD exposure models	Not exposed (n = 224,804), uncertain low-dose exposure (n = 75,717), exposed (n = 48,770)	Musculoskeletal system disease (vs not exposed): Uncertain low dose; < 0.013 mg-min/m^3; 0.013–0.097 mg-min/m^3; 0.097–0.514 mg-min/m^3	OR = 0.90 (95% CI 0.86–0.94) OR = 0.90 (95% CI 0.83–0.98) OR = 0.90 (95% CI 0.83–0.96) OR = 0.98 (95% CI 0.87–1.09)	Sex, age group, prewar hospitalization, race, service type, marital status, pay grade, occupation	See Smith et al. (2002); also, probable substantial exposure misclassification as models were revised, lack of a clear dose–response pattern, little biologic plausibility given that no effect was seen for nervous system diseases
Smith et al., 2003 (Vol. 8)	DoD hospitalization study (1991–2000); analysis of health	99,614 active-duty military considered exposed vs 318,458	First hospitalization for any musculoskeletal system disease	Exposed vs unexposed: RR = 0.99 (95% CI 0.96–1.02)	No adjustment for confounding exposures	Restricted to DoD hospitals; restricted to hospitalizations for only Gulf War veterans who remained on active duty

Study	Design	Population	Outcomes	Results	Adjustments	Comments
	outcomes and exposure to nerve agents (follow-up of Gray et al., 1999b)	nonexposed, according to revised DoD exposure model	(ICD-9-CM codes 710–739)			after the war

NOTE: CCEP = Comprehensive Clinical Evaluation Program; CDC = Centers for Disease Control and Prevention; CI = confidence interval; CFS = chronic fatigue syndrome; COSHPD = California Office of Statewide Health Planning and Development; CWP = chronic widespread pain; DMDC = Defense Manpower Data Center; DoD = Department of Defense; GWV = Gulf War veteran; HR = hazard ratio; ICD = International Classification of Diseases; IPGWSG = Iowa Persian Gulf War Study Group; NDV = nondeployed veteran; OR = odds ratio; PB = pyridostigmine bromide; PMR = proportional morbidity ratio; RR = risk ratio; UK = United Kingdom; U.S.= United States.

GENITOURINARY SYSTEM CONDITIONS

Major conditions and conditions evaluated in this section include kidney disease, urolithiasis (kidney stones), urinary tract infections, prostatitis, and sexual difficulties. Gynecologic outcomes including abnormal cervical pathology and inflammatory disease of the ovary are also assessed. Cancers of the genitourinary system such as testicular cancer are discussed in the section on cancer. All primary studies of conditions of the genitourinary system are summarized in Table 4-21 at the end of this section.

Summary of Volumes 4 and 8

Genitourinary outcomes were not addressed separately in Volume 4 of the *Gulf War and Health* series. The Volume 8 committee identified five primary studies of hospitalization for genitourinary system conditions, one other primary study that was not on hospitalization (Frommelt et al., 2000), and 10 secondary studies (mostly large surveys of self-reported outcomes). Frommelt et al. (2000) found that the evidence did not support an association between Gulf War deployment and cervical pathology using clinical confirmation of Pap smear results among female veterans in all age groups except women aged 26–30 who had a slight increase in "other than within normal limits," but the authors concluded that there was no biologically plausible evidence to support an age-specific association between deployment and abnormal cervical pathology.

In the 10 secondary studies, the prevalence of various self-reported genitourinary conditions was greater among Gulf War deployed veterans compared with nondeployed veterans (Gray et al., 2002; Kang et al., 2000, 2009; Page et al., 2005; Pierce, 2005; Proctor et al., 1998; Simmons et al., 2004; Steele, 2000; Unwin et al., 1999). In one study of the effects of exposure to nerve agents released by the Khamisiyah demolition, reporting of genitourinary conditions was similar in exposed and unexposed veterans (Page et al., 2005).

Five hospitalization studies, mostly in DoD hospitals, assessed conditions of the genitourinary system. Gray et al. (1996, 2000) and Smith et al. (2006) assessed the difference between deployed and nondeployed veterans, and two other studies examined the effects of environmental exposures to nerve agents or oil-well fires among Gulf War veterans (Smith et al., 2002, 2003). These studies suggest that excess hospitalization due to conditions of the genitourinary system did not occur among active-duty Gulf War veterans within the 10 years following the war. There is some suggestion that postwar hospitalizations for genitourinary conditions were similar among Gulf War deployed veterans who were and were not exposed to nerve agents or smoke from oil-well fires, but the results are not generalizable to the entire cohort of Gulf War veterans. Furthermore, by limiting such studies of genitourinary outcomes to hospitalizations, conditions that are not severe enough to require inpatient care were not assessed. Combining all genitourinary conditions into a single broad diagnostic category of "diseases of the genitourinary system" would also have limited the ability to detect associations with more specific, but etiologically distinct, outcomes.

The specific conditions being evaluated in surveys of Gulf War veterans have varied across studies, generally addressing frequency of urination, urinary tract infections, sexual problems, or broadly defined "disease of the genital organs." Secondary studies addressing deployment and genitourinary conditions are limited by self-reported outcomes, lack of clinical

confirmation, potential recall bias, and generally poor response rates. The discrepancies between hospitalization studies and survey studies of genitourinary outcomes may reflect variation in the severity and types of genitourinary outcomes ascertained by the different approaches; differences in active-duty, reserve, and former military personnel; the influence of reporting and selection biases; or the role of chance.

Studies of self-reported sexual dysfunction have included reports of decreased libido, erectile dysfunction, discomfort or pain during intercourse, and a burning sensation after sex. One primary study was discussed in Volume 4 that indicated deployed veterans reported more sexual problems than controls and problems were associated with traumatic events (having seen killed or wounded people, watched a friend or colleague being threatened or shot at, or having been threatened themselves) (Ishoy et al., 2001b).

The Volume 8 committee identified no new primary studies of sexual dysfunction in Gulf War veterans but did consider seven secondary studies (Gray et al., 2002; Iowa Persian Gulf Study Group, 1997; Page et al., 2005; Proctor et al., 1998; Simmons et al., 2004; Steele, 2000; Unwin et al., 1999). Gulf War veterans consistently reported an increased prevalence of sexual problems when compared with nondeployed veterans. The one study assessing exposures specific to Gulf War service reported no association between nerve agent exposure, and reported sexual problems among veterans deployed to the Gulf War (Page et al., 2005). With the exception of a single study that incorporated physician interviews to verify symptom reporting, studies of sexual problems have relied exclusively on self-reports. *The Volume 8 committee concluded there was inadequate/insufficient evidence to determine whether an association exists between Gulf War deployment and other specific conditions of the genitourinary system. The Volume 8 committee also concluded there was limited/suggestive evidence of an increased prevalence of self-reported sexual difficulties among Gulf War veterans.*

New Literature

The committee did not identify any new primary studies on the genitourinary system, including sexual dysfunction. However, Ishoy et al. (2001b) which assessed sexual difficulties in Danish Gulf War veterans, and was included in Volume 4 as a primary study in the section on male fertility problems, has been added to the table in this section.

Secondary Studies

The committee found two studies that met its criteria for a secondary study. Sim et al. (2015) reported on the Australian Gulf War Veterans' Follow Up Health Study, conducted between 2011 and 2013 (this study was a follow-up to the baseline study discussed in Volume 8). This study is an assessment of the entire 1,871 Australian Gulf War cohort 10 years after the 2000–2002 baseline study and 20 years after the war. Results were adjusted for age, rank category, and service branch. Of the 1,456 eligible deployed male veterans, 715 participated in the study and 675 of the 1,449 nondeployed veterans provided the comparison group. Deployed veterans were more likely to report physician-diagnosed kidney disease (RR = 1.83, 95% CI 0.95–3.35) and bladder disease (RR = 1.65, 95% CI 0.74–3.67), but the differences were not statistically significant.

Dursa et al. (2016) reported results from the third wave of the VA's cross-sectional National Health Study of Persian Gulf War Era Veterans that was conducted in 2012–2013 and asked 8,104 deployed and 6,148 Gulf War era veterans whether a doctor ever told the veteran

that they had "any disease of the genital organs" or "repeated bladder infections." The weighted prevalence of genital organ disease in the deployed was 5.1% and 4.6% in the era veterans (OR = 1.17, 95% CI 0.93–1.47); the weighted prevalence of repeated bladder infections was 2.4% and 2.8% in deployed and era veterans, respectively (OR = 1.00, 95% CI 0.76–1.33). ORs were adjusted for age, sex, race, service branch, unit, BMI, and smoking status.

Other Related Studies

VA provided a health care use report for Gulf War deployed and era veterans who sought care in VA facilities from October 2001 to December 2013. The report presented the prevalence of diagnoses of diseases by ICD-9 code categories, including diseases of the genitourinary systems (ICD-9 categories 580–629) (Table 4-22). 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. A total of 286,995 Gulf War deployed and 296,635 era veterans received treatment at VA over the approximately 11-year period (VA 2014a,b). These VA health care users represent 46% of all deployed Gulf War veterans and 36% of all nondeployed era veterans.

TABLE 4-22 Ten Most Frequent Genitourinary Diagnoses for Deployed and Nondeployed Gulf War Veterans Seeking Health Care in VA between 2002 and 2013

Diagnosis	Deployed N = 80,156 (%)	Nondeployed N = 82,231 (%)
Disorders of penis (607)	34.0	29.8
Other disorders of urethra, urinary tract (599)	24.9	25.3
Hyperplasia of prostate (600)	20.2	21.9
Calculus of kidney, ureter (592)	10.3	9.5
Chronic kidney disease (585)	8.2	8.2
Other disorders of male genital organs (608)	6.7	Not reported
Menopausal and postmenopausal disorders (627)	6.3	10.3
Other disorders of breast (611)	6.3	8.0
Other disorders of kidney, ureter (593)	6.2	9.5
Disorders of menstruation, other abnormal bleeding from female genital tract (626)	5.7	Not reported

SOURCE: VA (2014a,b).

Conclusions

The studies cited in Volume 8, particularly the secondary studies, found that Gulf War veterans reported more conditions and symptoms of the genitourinary system. The one secondary study identified by the Volume 10 committee indicated that deployed veterans were slightly but not significantly more likely to report having had a disease of the kidney or bladder.

Therefore, the Volume 10 committee concludes that there is inadequate/insufficient evidence to determine whether an association exists between Gulf War deployment and genitourinary conditions.

There was no new evidence to support or refute the association between self-reported sexual dysfunction and deployment in Gulf War veterans. The committee finds that given the aging of the Gulf War veterans and the unlikelihood that new genitourinary conditions will develop 25 years after the Gulf war that are attributable to their Gulf War service, it is doubtful that further assessments will show increased risk of these conditions.

Therefore, the Volume 10 committee concludes there is limited/suggestive evidence of an increased prevalence of self-reported sexual difficulties among Gulf War veterans.

TABLE 4-21 Conditions of the Genitourinary System

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Frommelt et al., 2000 (Vol. 8)	Retrospective cohort	1,446 female GWVs and 5,269 female NDVs with routine Pap smears conducted in 1994	Pap smear results	Nonnormal diagnosis more frequent in GWVs (11.5%) vs NDVs (6.6%) in 26–30 year old age group (p = 0.013); no significant difference in occurrence of nonnormal diagnoses detected in any other age group	5-year age groups (20–50, over 50), marital status, race, rank	
Gray et al., 1996 (Vol. 8)	Retrospective cohort, DoD hospitalizations from August 1991 through September 1993	547,076 active-duty GWVs, 618,335 NDVs	Hospital-discharge diagnoses of a disease of the genitourinary system in DoD hospital system (ICD-9 classification)	Any genitourinary disease (exact values not given) 1991: OR about 1.1 (95% CI 1.0–1.15); 1992 and 1993: ORs about 1.0 (95% CI 0.95–1.05) Inflammatory disease of ovary, fallopian tube, pelvic cellular tissue, and peritoneum: rate ratio = 1.35 (95% CI 1.11–1.63) Other disorders of the breast: rate ratio = 1.30 (95% CI 1.03–1.63) Redundant prepuce and phimosis: OR = 1.59 (95% CI 1.22–2.07) Infertility, female: rate ratio = 1.59 (95% CI 1.19–2.11)	Prewar hospitalization, sex, age, race, service branch, marital status, rank, length of service, salary, occupation	Very short follow-up period; no outpatient data; restriction to DoD hospitals, and thus to persons remaining on active duty after the war; no adjustment for potential confounders such as smoking
Gray et al., 2000 (Vol. 8)	Retrospective cohort, hospitalizations from August 1991	652,979 GWVs, 652,922 randomly selected NDVs	Hospital-discharge diagnoses of a disease of the genitourinary	DoD PMR = 1.01 (95% CI 0.98–1.03); VA PMR = 0.96 (95% CI 0.87–0.1.05);	Age, sex, race (only for DoD PMR)	Able to assess only illnesses that resulted in hospitalization; possible undetected

Study	Design	Population	Outcomes	Results	Adjustments	Comments
	through December 1994	182,164 DoD hospitalizations; 16,030 VA hospitalizations; 5,185 COSHPD hospitalizations	system in DoD, VA, and COSHPD hospital systems	COSHPD PMR = 0.80 (95% CI 0.59–1.00)		confounders PMR has lower sensitivity than a comparison of hospitalization rates
Ishoy et al., 2001b (Vol. 4)	Cross-sectional (elaboration of findings in Ishoy et al., 2001a)	Danish Gulf War Study: 661 GWVs , 215 NDVs	Self-reported sexual problems	Male GWVs vs NDVs: sexual problems (80% decreased libido), 79 vs 8 (OR = 2.9, 95% CI 1.4–6.0)	Age	Limitations: small study, self-reported soft outcomes and exposures
Smith et al., 2006 (Vol. 8)	Retrospective cohort study of DoD hospitalizations (cohort data from DMDC)	Active-duty personnel with a single deployment to: Gulf War theatre (n = 455,465); southwest Asia peacekeeping mission, 1991–1998 (n = 249,047); Bosnia, 1995–1998 (n = 44,341)	Postdeployment hospitalization events (1991–2000) for an ICD-9-CM diagnosis of a disease of the genitourinary system (580–629) and nephritis specifically	Compared with GWVs, veterans of Bosnia showed reduced risk (HR = 0.60, 95% CI 0.51–0.70), and veterans of southwest Asia showed similar risk (HR = 1.00, 95% CI 0.92–1.09) Nephritis, Bosnia: HR = 0.47 (95% CI 0.20–1.08); southwest Asia: HR = 1.30 (95% CI 0.84–2.01)	Sex, age, marital status, pay grade, race/ethnicity, service branch, occupation, and predeployment hospitalization; time-dependent covariate to account for changing hospitalization methods, diagnostic criteria, and procedures	Lower hazard ratio observed in veterans of Bosnia may be partially explained by better access to care in theater Active-duty personnel only; hospitalizations at DoD facilities only; no outpatient data

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Smith et al., 2002 (Vol. 8)	Retrospective cohort study of DoD hospitalizations 1991–1999; exposure modeling for oil-well fire smoke	405,142 GWVs who were in theater during the time of Kuwaiti oil-well fires	Hospitalization for diseases of the genitourinary system	Risk was not increased at any level of smoke plume exposure	Adjusted for "influential covariates," defined as demographic or deployment variables with *p* values less than 0.15	Objective measure of disease not subject to recall bias; no issues with self-selection; however, only DoD hospitals, only active duty, no adjustment for other potential confounders
Smith et al., 2003 (Vol. 8)	Retrospective cohort study of DoD hospitalizations (1991–2000); analysis of health outcomes and exposure to nerve agents (follow-up of Gray et al., 1999b)	99,614 active-duty GWVs considered exposed vs 318,458 nonexposed, according to revised DoD exposure model	Hospitalization for any disease of the genitourinary system (ICD-9-CM codes 580–629)	RR = 0.96 (95% CI 0.91–1.00)		Restricted to DoD hospitals; restricted to hospitalizations for only Gulf War veterans who remained on active duty after the war; no adjustment for confounding exposures

NOTE: CI = confidence interval; COSHPD = California Office of Statewide Health Planning and Development; DU = depleted uranium; DMDC = Defense Manpower Data Center; DoD = Department of Defense; GWV = Gulf War veteran; HR = hazard ratio; MRR = mortality rate ratio; NDV = nondeployed veteran; OR = odds ratio; PHQ = Patient Health Questionnaire; PMR = proportional morbidity ratio; RR = risk ratio; VA = Department of Veterans Affairs.

ADVERSE REPRODUCTIVE AND PERINATAL OUTCOMES

This section evaluates the findings on birth defects in the offspring of veterans, adverse pregnancy outcomes, and infertility. As appropriate, the major results from each study are addressed by whether the father or the mother served in the Gulf War and by outcome. Sexual dysfunction is discussed in the previous section on conditions of the genitourinary system even though it may affect one's ability to reproduce. All primary studies of adverse reproductive and perinatal outcomes are summarized in Table 4-23 at the end of this section.

Birth Defects

Birth defects occur in about 3% of live births. The numerous types of serious or disabling birth defects include structural defects, chromosomal abnormalities, and birth defect syndromes (California Birth Defects Monitoring Program, 2009). Because of that diversity, epidemiologists attempting to calculate whether birth defects are increased in a particular group such as deployed veterans, sometimes encounter the problem of making multiple comparisons; that is, the greater the number or the more types of comparisons, the greater the likelihood that one or more of them will appear significant when no true differences exists. Several statistical techniques are used to adjust for or minimize the problem of multiple comparisons, but they are not foolproof.

Summary of Volumes 4 and 8

In Volume 4, one primary study (Araneta et al., 2003) and five secondary studies (Cowan et al., 1997; Doyle et al., 2004; Goss Gilroy Inc., 1998; Kang et al., 2001; Penman et al., 1996) were reviewed. Some evidence of increased risk of birth defects among offspring of Gulf War veterans was reported primarily on the basis of two studies (Araneta et al., 2003; Doyle et al., 2004); however, with the possible exception of urinary tract abnormalities, the increased prevalence estimates of specific defects in the two studies were not consistent. The reported association of Gulf War service with Goldenhar syndrome, a rare craniofacial abnormality, was inconclusive (Werler et al., 2005). Thus, the Volume 4 committee concluded that there is no consistent pattern of higher prevalence estimates of birth defects among offspring of male or female Gulf War veterans and that no single defect, except urinary tract abnormalities, had been found in more than one well-designed study.

The Volume 8 committee identified three additional secondary studies (Ishoy et al., 2001a; Kelsall et al., 2007; Verret et al., 2008) that reported data on birth defects in association with the Gulf War; however, no additional support for an association between birth defects and deployment to the Gulf War was reported. Few cases made detection of any differences between birth defect risks in deployed and nondeployed veterans difficult. Overall, studies of Gulf War service and congenital malformations were problematic because specific birth defects are relatively rare, multiple comparisons were performed, and sample sizes were small when divided by timing of exposure (before or after conception) and whether the mother or the father was exposed. Thus, the Volume 8 committee repeated the conclusion of the Volume 4 committee. *The Volume 8 committee concluded there was inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and specific birth defects.*

Adverse Pregnancy Outcomes

Studies of adverse pregnancy outcomes have evaluated the prevalence of spontaneous abortions, stillbirths, ectopic pregnancies, preterm births, low birth weight, and macrosomia in the pregnancies of Gulf War deployed and nondeployed men and women.

Summary of Volumes 4 and 8

The Volume 4 committee reviewed one primary study of hospital-discharge data suggestive of an increased risk of spontaneous abortions and ectopic pregnancies (Araneta et al., 2004). However, those results may not be generalizable to deployed women who left the service or to pregnancy-related admissions to nonmilitary hospitals. Thus, the Volume 4 committee found it difficult to conclude whether there is a higher prevalence of adverse pregnancy outcomes in Gulf War deployed than in nondeployed veterans. Two secondary studies of self-reported adverse birth outcomes indicated possible increased risks of miscarriage, spontaneous abortions, and stillbirths among pregnancies to fathers deployed to the Gulf War, but results were not consistent between the studies (Doyle et al., 2004; Kang et al., 2001).

Five additional secondary studies evaluating the effect of deployment on adverse pregnancy outcomes were identified by the Volume 8 committee; all of these studies were based on self-reported data (Ishoy et al., 2001a; Kang et al., 2009; Kelsall et al., 2007; Verret et al., 2008; Wells et al., 2006). Findings for spontaneous abortion were not replicated in the four secondary studies of female veterans, which used self-reported outcome data (Ishoy et al., 2001a; Kang et al., 2009; Wells et al., 2006; Kelsall et al., 2007). Similarly, only one secondary study assessed ectopic pregnancies and observed no differences by deployment status among male or female veterans (Wells et al., 2006). Among males, no consistent associations with Gulf War deployment were observed for spontaneous abortion, preterm birth, or low birth weight, although three studies reported modest increases in self-reported miscarriages among partners of deployed males (Kang et al., 2009; Wells et al., 2006; Kelsall et al., 2007). *The Volume 8 committee concluded there was inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and adverse pregnancy outcomes such as miscarriage, stillbirth, preterm birth, and low birth weight.*

Fertility

Studies of fertility problems have assessed semen parameters, hospitalization for infertility or genitourinary system conditions, self-reported difficulties achieving a pregnancy, and serum concentrations of reproductive hormones in males. Infertility is typically defined as trying to conceive unsuccessfully for 12 months or more after discontinuing contraception, although the quality of the outcome measurement has varied across studies and has included inference from self-reported disorders of infertility or sperm abnormalities, reports of having difficulty getting pregnant, reports of consulting a doctor after trying unsuccessfully for more than 1 year, and seeking treatment for childlessness.

Summary of Volumes 4 and 8

The Volume 4 committee reviewed two primary studies (Ishoy et al., 2001a,b; Maconochie et al., 2004). For the most part, the findings on fertility and sexual problems relied on self-reports. There was no evidence of statistically significant differences in concentrations of male reproductive hormones between Gulf War deployed veterans and nondeployed veterans.

While self-reported infertility was increased among deployed veterans versus nondeployed veterans and deployed veterans reported a longer time to conception, few cases could be verified with clinical diagnostic information, and information about partners' fertility status was lacking. The Volume 4 committee concluded that although it appears that there is no difference in the prevalence of male fertility problems or infertility between the deployed Gulf War veterans and their nondeployed counterparts, it was difficult to draw conclusions from the small number of available studies.

The Volume 8 committee identified three secondary studies (Kang et al., 2009; Kelsall et al., 2007; Verret et al., 2008). It found no evidence of significant differences in concentrations of male reproductive hormones between deployed and nondeployed Gulf War veterans. Although changes in hormonal concentrations and semen characteristics are reproductive outcomes of interest, they are not definitive indicators of infertility (with the exception of azoospermia). *The Volume 8 committee concluded there was inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and fertility problems.*

New Literature

Only two studies reporting on reproductive outcomes were identified: one primary study of birth defects (Bukowinski et al., 2012) and one secondary study of self-reported pregnancy, fertility, and adverse birth outcomes (Sim et al., 2015).

Primary Study

Bukowinski et al. (2012) identified 178,766 infants in the DoD Birth and Infant Health Registry born between 1998–2004 with at least one parent who was in the military during the Gulf War era (26,617 born to female veterans and 159,446 born to male veterans). Rates of birth defects among infants born to deployed veterans were compared with those among nondeployed veterans. The investigators studied eight specific birth defects: the five most common in the study population (atrial septal defect, ventricular septal defect, patent ductus arteriosus, hypospadias/epispadias, and congenital hip dislocation), and three previously reported to be associated with deployment (aortic valve stenosis, hypoplastic left heart syndrome, and renal agenesis/dysgenesis). Exposure information was collected from DoD databases pertaining to deployment, exposure to nerve agents at Khamisiyah and oil-well fires, and in-theater hospitalizations. Analyses were stratified by which parent was deployed, and regression models were adjusted for effects of infant gender, preterm birth, maternal and paternal age, race/ethnicity, branch of service, pay grade, and occupation. There was no association between being deployed and any of these birth defects (OR = 1.05, 95% CI 0.86–1.28), nor were there any statistically significant increases in specific birth defects for deployed versus era females or males. However, there was a slight increase in birth defects in children born to men who had been deployed for 153–200 days (OR = 1.25, 95% CI 1.05–1.49), but not for a shorter or longer period. Birth defects were not associated with any other exposures. This study may be limited by its use of registry data to identify occurrences of birth defects; use of the DoD registry will miss births to veteran parents who left the military.

Secondary Study

Sim et al. (2015) reported on the Australian Gulf War Veterans' Follow Up Health Study, conducted between 2011 and 2013 (this study was a follow-up to the Kelsall et al. (2004b) baseline study discussed in Volumes 4 and 8). This study is an assessment of the entire

Australian Gulf War cohort 10 years after the 2000–2002 baseline study and 20 years after the war. Results were adjusted for age, rank category, and service branch, but not for smoking. Of the 1,456 eligible deployed veterans, 715 participated in the study and 675 of the 1,449 nondeployed veterans provided the comparison group. Based on self-reported pregnancy and fertility information collected since 1992, more deployed veterans reported difficulty fathering a pregnancy (RR = 1.44, 95% CI 1.05–1.99), but they have not sought or undertaken treatment or been less likely to have actually fathered a pregnancy since then. Also, deployed veterans reported more doctor-diagnosed impotence (RR = 2.06, 95% CI 1.30–3.29). No differences in reported live births, miscarriage, stillbirth, termination, premature births, or low birthweight were found.

Conclusions

Very little new information on reproductive and birth effects was available to the Volume 10 committee. The one primary study is limited by its use of registry data, which may not be representative of all Gulf War veterans, and the one secondary study is limited by its use of self-reported information collected more than 20 years after the Gulf War. Regardless of their limitations, the results of those studies are in concurrence with studies described in previous volumes in that no increased risks of birth defects or adverse pregnancy or birth outcomes were reported for deployed male or female Gulf War veterans. Self-reported information indicates possible male infertility, but the evidence is not strong enough to warrant any change to the Volume 8 conclusions. Furthermore, most studies of Gulf War deployment and infertility have relied on self-reports that give rise to a substantial opportunity for recall bias. Few studies have examined the question of fertility among female veterans.

The committee finds that given that female Gulf War veterans are past childbearing age, and the unlikelihood that new birth defects, adverse pregnancy outcomes, and fertility conditions will develop 25 years after the Gulf war that are attributable to their Gulf War service, it is doubtful that further assessments will show increased risk of these conditions.

Therefore, the Volume 10 committee concludes there is inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and specific birth defects. It further concludes there is inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and adverse pregnancy outcomes such as miscarriage, stillbirth, preterm birth, and low birth weight.

The Volume 10 committee also concludes there is inadequate/insufficient evidence to determine whether an association exists between deployment to the Gulf War and fertility problems.

TABLE 4-23 Birth Defects, Adverse Pregnancy Outcomes, and Fertility

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Volume 4 and 8 Primary Studies						
Birth Defects						
Araneta et al., 2003 (Vol. 4)	Retrospective cohort, using population-based, birth-defect registries (active surveillance all cases identified from birth to 1 year)	Infants of military personnel born 1/1/1989–12/31/1993 in Arizona, Iowa, Hawaii, and participating counties of Arkansas, California, Georgia to 450 GWV mothers 3,966 NDV mothers 11,511 GWV fathers 29,086 NDV fathers	48 birth defects identified by CDC as occurring frequently or of public health importance, excluding pulmonary artery anomalies and adding dextrocardia, chromosomal anomalies (other than trisomies 13, 18, and 21), and Goldenhar syndrome	Postwar conceptions, GWVs vs NDVs (unadjusted RRs): father: tricuspid valve insufficiency, 10/4,648 vs 9/11,164 (RR = 2.7, 95% CI 1.1–6.6); aortic valve stenosis, 5/4,648 vs 2/11,164 (RR = 6.0, 95% CI 1.2–31.0); coarctation of aorta, 5/4,648 vs 3/11,164 (RR = 4.0, 95% CI 0.96–16.8); renal agenesis or hypoplasia, 5/4,648 vs 5/11,164 (RR = 2.4, 95% CI 0.7–8.3) mother: hypospadias 4/154 vs 4/967 (RR = 6.3, 95% CI 1.5–26.3) GWVs postwar vs prewar conceptions (unadjusted RRs): father: aortic valve stenosis 5/4,648 vs 0/6,863 (RR = 16.3, 95% CI 0.9–294); coarctation of aorta, 5/4,648 vs 1/6,863 (RR = 7.4, 95% CI 0.9–63.3); renal agenesis and hypoplasia, 5/4,648 vs 0/6,863 (RR = 16.3, (95% CI 0.9–294); adjustment did not change results	State, maternal and paternal age, race, marital status, education, plurality, parity, prenatal visits, gestational weight gain, branch of service, military rank, prenatal alcohol exposure, intrauterine growth retardation, low birth weight, small for gestational age, preeclampsia	California limited to diagnoses in nonmilitary hospitals; relies on availability of unique personal identifiers in military and birth certificate data, limited power to assess individual defects, multiple comparisons, limited to live births Population- based, including reservists, National Guard, former military personnel; includes defects diagnosed through first year, medically confirmed diagnoses, comparisons with prewar experience

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Werler et al., 2005 (Vol. 4)	Case-control	HFM cases ≤ 3 years old (born 1996–2002) from craniofacial clinics in 24 U.S. cities (n = 232); controls matched by age and pediatrician (n = 832)	HFM, facial asymmetry, or Goldenhar syndrome and no evidence of Mendelian inherited or chromosomal anomaly	Adjusted ORs: parental army service, OR = 2.4 (95% CI 1.4–4.2); parental GW army service, OR = 2.8 (95% CI 0.8–9.6); any parental GW service, OR = 0.8 (95% CI 0.3–2.3)	Family income, race, BMI in early pregnancy, multiple gestation	No adjustment for lifestyle factors Included cases diagnosed up to of 3 years age
Doyle et al., 2004 (Vol. 8)	Retrospective cohort	All UK GWVs and randomly selected cohort of NDVs responding to postal questionnaire; conceptions from postdeployment (for NDVs—conceived after 1/1/1991) through 11/8/1997 16,442 GWV fathers 11,517 NDV fathers 484 GWV mothers 377 NDV mothers External comparison populations: (1) NIFS; (2) annual registered stillbirths in England and Wales, 1991-1998	Fetal death: early and late miscarriage, stillbirth; congenital malformations excluding minor abnormalities among live births; self-report with clinical confirmation attempted for fetal deaths and live births with reported abnormalities	Adjusted ORs GWVs vs NDVs: fathers: all miscarriages 2,829/15,539 vs 1,525/10,988 (OR = 1.4, 95% CI 1.3–1.5); any congenital malformation, 686/13,191 vs 342/9,758 (OR = 1.5, 95% CI 1.3–1.7); other malformations of digestive system, 69/13,191 vs 31/9,758 (OR = 1.6, 95% CI 1.0–2.5); genital system, 45/13,191 vs 19/9,758 (OR = 1.8, 95% CI 1.0–3.0); urinary system, 103/13,191 vs 48/9,758 (OR = 1.6, 95% CI 1.1–2.3); musculoskeletal system, 194/13,191 vs 78/9,758 (OR = 1.8, 95% CI 1.4–2.4); other nonchromosomal malformations, 45/13,191 vs 19/9,758 (OR = 1.7, 95% CI 1.0–3.0); cranial neural crest, 184/13,191 vs 101/9,758 (OR = 1.3, 95% CI 1.0–1.7);	Stratum matched on branch of service, sex, age, serving status, rank; ORs adjusted by year of pregnancy end, paternal/maternal pregnancy order, maternal age, service, rank, previous fetal death, multiplicity	Response rates: GWVs: men 53%, women 72%; NDVs: men 42%, women 60% Poor response rates among men and response rates lower in NDVs, low numbers of miscarriages in NDVs compared with NIFS population could mean participation and reporting bias; multiple comparisons Medical confirmation for some cases; fetal deaths as well as live births; external comparison groups

Study	Design	Population	Outcomes	Results	Adjustments	Comments
				metabolic and single gene defects, 22/13,191 vs 8/9,758 (OR = 2.0, 95% CI 0.9–4.8); mothers: no significant associations		to evaluate possible biases
Adverse Pregnancy Outcomes						
Araneta et al., 2004 (Vol. 4)	Retrospective cohort	Deployed women admitted to military hospitals for pregnancy-related diagnoses (including live births, abortions, ectopic pregnancies, pregnancy-related complications) from 8/2/1990 to 5/31/1992 and who responded to mailed survey: GW-exposed conceptions (n = 415), GW postwar conceptions (n = 298), NDVs (n = 427)	Self-reported stillbirths, spontaneous abortions, ectopic pregnancies, pregnancy-related complications (ICD-9-CM codes 640–676); confirmed by discharge diagnostic data	Adjusted RRs: mothers: GWV vs NDV postwar conceptions: spontaneous abortions, 68 vs 39 (RR = 2.92, 95% CI 1.87–4.56); ectopic pregnancies, 32 vs 6 (RR = 7.70, 95% CI 3.00–19.8); GWV vs NDV exposed conceptions: spontaneous abortions, 48 vs 39 (RR = 1.44, 95% CI 0.91–2.29); ectopic pregnancies, 10 vs 6 (RR = 1.91, 95% CI 0.67–5.46)	Age, race, education, marital status, branch of service, military rank, parity, history of adverse outcome	Overall response rate: 50% Low response rate; no information on smoking, alcohol, caffeine, other known risk factors for fetal loss; possible limited generalizability due to restriction to military hospital admissions; recall bias Confirmation with discharge data, assessed GW-exposed and postwar conceptions
Fertility						
Ishoy et al., 2001a (Vol. 4)	Cross-sectional	Danish Gulf War Study, 661 GWVs 215 NDVs	Self-reports of sexual problems (including reduced libido); measured male reproductive	Male GWVs vs NDVs: self-reported sexual problems, 12.0% vs 3.7% ($p < 0.001$); reproductive hormones, no significant difference;	Age; BMI available; stratified on deployment organization, duration of	Participation rates: GWVs, 83.6%; NDVs, 57.8% Limited control for

Study	Design	Population	Outcomes	Results	Adjustments	Comments
			hormones: serum concentrations of LH, FSH, testosterone, inhibin B	suspected oligospermia, FSH ≥ 10 IU/L, inhibin B ≤ 80 pg/mL, 1.6% vs 1.6%; fertility rates, spontaneous abortion, congenital malformations: no differences	deployment	confounding, small numbers for study of fertility rates, congenital malformations; objective measurement of hormones
Maconochie et al., 2004 (Vol. 4)	Retrospective cohort (same cohort as Doyle et al., 2004)	Male UK veterans fathering or trying to father pregnancies after GW and before 8/97 10,465 GWV 7,376 NDV	Self-reported fertility problems: tried unsuccessfully for > 1 year and consulted doctor; type I infertility: never achieving pregnancy; type II infertility: never achieving live birth; semen quality; time to conception; attempted clinical confirmation from both partners' physicians	Adjusted ORs GWVs vs NDVs: fertility problems, 732 vs 370: (OR = 1.38, 95% CI 1.20–1.60); type I 259 vs 122 (OR = 1.41, 95% CI 1.05–1.89); type II 356 vs 166 (OR = 1.50, 95% CI 1.18–1.89); time to conception > 1 year for planned pregnancies, 845/9,968 vs 528/7,408 (OR = 1.18, 95% CI 1.04–1.34) (increase in risk stable with time since GW)	Maternal and paternal age at first infertility consult or post-GW conception, year of first consult or conception, pre-GW pregnancy history, military service and rank, smoking, alcohol, pregnancy order	Response rates: GWVs, 53%; NDVs, 42% Limitations: low response rates, possible recall bias, clinically evaluated only 40% Strengths: attempted clinical evaluation, information on nonresponders available
Volume 10 Primary Study						
Bukowinski, et al., 2012	Cross-sectional	178,766 infants in DoD Birth and Infant Health Registry born between 1998–2004	Birth defects diagnosed in first year of life: five most prevalent	No association between being deployed and birth defect (OR = 1.05, 95% CI 0.86–1.28) No statistically significant	Adjustments for infant gender, parental age at birth, preterm birth,	Assessed for modeled exposure to smoke from oil-well fires and nerve

Study	Design	Population	Outcomes	Results	Adjustments	Comments
		with at least one parent who was GWV (26,617 born to female GWV and 159,446 born to male GWV)	and three reported to be increased in children of deployed GWV	increases in any birth defects for GWV vs NDV females or males: ventricular septal defect; atrial septal defect; aortic valve stenosis; hypoplastic left heart syndrome; patent ductus arteriosus; renal agenesis/dysgenesis; hypospadias and epispadias; and congenital hip dislocation Slight increase in birth defects in children born to men who had been deployed for 153–200 days (OR = 1.25, 95% CI 1.05-1.49) but not for a shorter or longer period Birth defects were not associated with any other exposures	race/ethnicity, branch of service, pay grade, occupational category	agents from Khamisiyah, in theater hospitalization, and length of deployment, including during major combat period

NOTE: BMI = body mass index; CDC = Centers for Disease Control and Prevention; CI = confidence interval; DU = depleted uranium; FSH = follicle-stimulating hormone; GW = Gulf War; GWV = Gulf War veteran; HFM = hemifacial microsomia; LH = luteinizing hormone; NDV = nondeployed veteran; NIFS = Nuclear Industry Family Study; OR = odds ratio; RR = risk ratio.

CAUSES OF MORTALITY

This section evaluates the findings on external and disease-related causes of death among Gulf War veterans. External causes of mortality include deaths due to motor vehicle accidents and crashes, and homicides and suicides. Studies of veterans of other wars, such as the Vietnam War, have found increased mortality from external causes, particularly in the years immediately following deployment (IOM, 2006). Disease-related causes of death include cancers, cardiovascular disease, and conditions of other organ systems.

In Volumes 4 and 8, only external causes of mortality were considered as a separate outcome; information on disease-related mortality was considered for each organ system when available. However, given the small number of new studies that have assessed mortality from any cause, this committee believed that it was reasonable to consider all causes of mortality in one section, the better to determine if deployed Gulf War veterans were at increased risk of dying compared with nondeployed veterans or with the general U.S. population. Therefore, this section begins with a brief description of the three new primary and one new secondary studies of mortality from a variety of outcomes that are cited for external causes and each relevant disease-related outcome later in this section. All primary studies on mortality are summarized in Table 4-24 at the end of this section.

New Mortality Literature

Three new primary studies of mortality were identified by the committee as well as one presentation from VA, which was considered to be a secondary study. Two studies were conducted on UK Gulf War veterans (UK Ministry of Defence, 2014; Knapik et al., 2009) and the third was a follow-up study of Australian Gulf War veterans (Sim et al., 2015). The first study, a statistical report from the UK Ministry of Defence, compared mortality rates for 53,409 deployed and 53,143 nondeployed (era) UK veterans from April 1, 1991 through December 31, 2013. Groups were similar based on age, gender, service component, regular versus reservist status, and rank. Mortality rate ratios (MRRs) and standardized mortality ratios (SMRs) (see Box 2-1 for definitions of statistical terms) were calculated for the two veteran groups and also for each veteran group and the general UK population adjusted for age, sex, and year. Cause of death was provided by the National Health System Information Centre for Health and Social Care and the National Office of Statistics for deaths that occurred in England and Wales, the General Register Office for deaths that occurred in Scotland, and the Northern Ireland Statistics Research Agency for deaths that occurred in Northern Ireland. These data have been used for all calculations where the veteran cohorts are compared to the UK population. Defence Statistics receives quarterly updates from each of these sources.

Over the 22-year follow-up period, a total of 1,506 deaths occurred among deployed veterans and 1,627 deaths occurred among era veterans; the difference in deaths between the groups was not statistically significant (MRR = 0.95, 95% CI 0.88–1.02). Causes of death were presented by total, all-cause coded, disease-related and major subcategories (e.g., neoplasms, infectious and parasitic diseases, conditions of the nervous system, conditions of the circulatory system, conditions of the respiratory system, conditions of the gastrointestinal system, and all other disease-related causes), and external causes including major categories and specific causes when available. Selected categories were compared for the veterans groups and the general UK

population. These comparisons were limited to all causes, all disease-related, neoplasms overall, circulatory system conditions as a category, all external causes, suicide and open verdict (deaths where intent could not be definitively proved), and transportation accidents (these include motor vehicle, motorcycle, pedestrian, train, airplane, air and space, water, and other). Specific results are presented below under each category.

The second primary study examined only external causes of death and was a systematic review of postdeployment mortality from injuries (Knapik et al., 2009). Although no new data were collected, the authors performed a meta-analysis of 20 studies (identified from a database search) of both Vietnam and Gulf War service members. Postdeployment injury mortality was assessed using ICD-9-CM E-codes E800–E999 (external causes of injury). Five of the studies were specific to Gulf War veterans and were retrospective cohort studies.

The third primary study was the Australian Gulf War Veterans' Follow Up Health Study (Sim et al., 2015). It updated all-cause and cause-specific mortality through 2010 in the entire cohort of 1,871 Australian Gulf War veterans and a comparison group of 2,922 veterans, frequency matched based on age, rank, and branch of service. Mortality data was obtained from the Australian National Death Index and included the date of death and all ICD-9 and ICD-10 coded underlying causes of death. Results were adjusted for age, rank category, and service branch, but not for smoking. A total of 108 deaths (2.3%) were reported for the entire cohort, and because this was such as small percentage of the cohort, categories of mortality were limited to all cause, overall external causes, intentional self-harm, transport accidents, cancer, and cardiovascular disease. Women veterans made up 2% of the deployed cohort, but because no women in either group had died during the 20-year follow-up, they were excluded from the mortality analyses.

The Volume 10 committee also was provided a presentation from VA on the most recent results of third survey wave of the cross-sectional National Health Study of Persian Gulf War Era Veterans (Bossarte, 2014). Although the data are not published and have not been peer reviewed, the committee found the information presented by VA to be useful and therefore discusses it here. The cohort consisted of 621,902 Gulf War veterans who served in the Persian Gulf between August 1, 1990, and March 1, 1991, and 746,248 veterans who served during this time, but were not deployed. The follow-up period spanned 20 years; for deployed veterans, follow-up began the year they left the theater, for nondeployed veterans, follow-up began May 1, 1991. For both groups, follow-up ended on the date of death or December 31, 2011. Cause of death was obtained from the National Death Index. A total of 21,144 deaths occurred in the deployed group and 29,340 deaths in the nondeployed group. Using the U.S. population (1960-2009) as the reference group, both deployed and nondeployed veterans had statistically significantly lower standardized mortality ratios (SMRs) for all-cause deaths (SMR deployed = 0.53, 95% CI 0.52–0.53; SMR nondeployed = 0.54, 95% CI 0.53–0.54); mortality rates for the deployed and nondeployed veterans were adjusted for age, sex, race, branch of service, and unit component. However, the committee notes that these findings should be interpreted with caution as using a 50-year span of non-age–adjusted mortality in the general U.S. population is not the most appropriate comparison group. The five most frequent causes of death were the same for both groups of veterans: malignant neoplasms, heart disease, transportation injuries, intentional self-harm, and other injury (major).

External Causes

Summary of Literature from Volumes 4 and 8

The Volume 4 committee reviewed four primary and two secondary studies that examined external mortality in Gulf War veterans, but all had numerous limitations. Although there were no statistically significant findings after adjustment for age, sex, race, and year of death, some studies suggested a modest increase in transportation-related deaths among deployed Gulf War veterans compared with nondeployed veterans in the first several years after the war (DASA, 2005; Kang and Bullman, 1996, 2001; Macfarlane et al., 2000; Writer et al., 1996).

The Volume 8 committee identified five new primary studies and two secondary studies reporting on external causes of mortality among U.S., Canadian, and UK veterans. The Canadian and UK studies were small, reflecting the relatively small number of personnel deployed from these countries. In the UK study, a previously reported increase in mortality from external causes had essentially disappeared with an additional 5 years of follow-up (Macfarlane et al., 2005). In the Canadian study, there was an excess of deaths from air and space transportation-related crashes among Gulf War veterans, but the authors suggest that this may have been due to greater employment of veterans in flight-related occupations (Statistics Canada, 2005). New studies concerning fatal motor vehicle accidents in U.S. Gulf War veterans found that younger age, lower education, and not using seatbelts or other restraints were risk factors for these events (Lincoln et al., 2006). The Volume 8 committee found that the studies provided evidence of a modestly higher mortality from all transportation-related causes among Gulf War deployed veterans compared with era veterans. In U.S. veterans, the excess was largely due to motor vehicle accidents specifically, which diminished and perhaps disappeared over time. *The Volume 8 committee concluded that there was limited/suggestive evidence of an association between deployment to the Gulf War and an increase in mortality from external causes, primarily motor vehicle accidents, in the early years after deployment.*

New Literature

Primary Studies

The UK Ministry of Defence (2014) statistical report listed categories of external causes of mortality including transportation accidents, overall and with additional subcategories of car, pedestrian, motorcycle, air and space, water, and other; accidental injuries including falls, inanimate mechanical forces, poisonings, and exposures; intentional self-harm and events of undetermined intent; assault; and legal interventions and operations of war. No statistically significant difference in mortality rates was found for any of the categories or subcategories of external causes between deployed and nondeployed UK veterans. However, when the overall SMRs[14] were calculated that compared deployed and nondeployed veterans to the age- and gender-adjusted UK population from 1991 to 2013, the veterans of both groups had a statistically significant decreased risk of dying overall (SMR deployed = 0.60, 95% CI 0.57–0.63; SMR nondeployed = 0.64, 95% CI 0.61–0.67), but they had increased rates of deaths from transportation accidents (SMR deployed = 1.86, 95% CI 1.63–2.13; SMR nondeployed = 1.61, 95% CI 1.39–1.86). The authors further investigated the increased risk of dying from transport

[14] Although the UK Ministry of Defence and Sim et al. (2015) both present standardized mortality ratios and hazard ratios multiplied by 100, the committee presents the results on a 1.0 scale to be consistent with the more common practice as well as to make comparisons with the U.S. literature easier.

accidents in both veteran cohorts compared with the age- and gender-standardized UK population. SMRs were calculated using 3-year moving averages for each year from 1991 to 2013. The SMR for all causes of death and deaths due to external causes peaked in 1992 and remained elevated in the years immediately following the Gulf War as previously reported in Volumes 4 and 8.

The meta-analysis performed by Knapik et al., (2009) only examined death from external causes, that is, motor vehicle accidents, suicide, homicide, and all other external causes. The authors reported summary mortality rate ratios[15] (SMRR). Injury-related mortality was increased for deployed UK veterans vs nondeployed veterans (SMRR = 1.26, 95% CI 1.16–1.37) during the 3 to 8 years of follow-up. Much of the excess mortality among deployed veterans was associated with motor vehicle events (SMRR = 1.39, 95% CI 1.22–1.60). At 7 to 13 years of follow-up, excess mortality appeared to decrease, but mortality rates for all external causes and motor vehicle events remained statistically significantly higher among the deployed veterans (SMRR external causes = 1.09, 95% CI 1.04–1.14 and SMRR motor vehicle = 1.29, 95% CI 1.18–1.40). No statistically significant difference between deployed and nondeployed veterans was found for suicide or homicide. However, two of the studies used in the meta-analysis (Kang and Bullman, 1996, 2001) stratified mortality rates by gender and found that female Gulf War veterans had statistically significantly higher adjusted MRRs for all external causes and the specific subcategories of motor vehicle events, suicide, and homicide, compared with male veterans. The authors did not examine other causes of death included in all external causes, such as falls, firearms, poisoning, or asphyxiation. The committee notes that the authors used the entire range of external cause codes (E800–E999) without eliminating accidental poisoning (E850–E869), adverse effects of therapeutic drugs (E930–949), medical misadventure during surgical and medical care (E870–E876), and injuries resulting from operations of war (E990–E999). Therefore, the individual studies that assessed mortality postdeployment might have contributed to misclassification errors when considered in aggregate in the meta-analysis.

In the Australian Gulf War Veterans' Follow Up Health Study (Sim et al., 2015) the all-cause mortality and all-external cause mortality were lower for both veterans cohorts compared with the Australian male population, but the differences were statistically significant only for the era veterans (all-cause SMR = 0.59, 95% CI 0.45–0.76; all external causes SMR =0.61, 95% CI 0.41–0.92), but not the deployed veterans (all cause SMR = 0.77, 95% CI 0.58–1.02; all external causes SMR = 0.70, 95% CI 0.43–1.13). No statistically significant differences between the deployed or era veterans and the Australian male population were found for intentional self-harm or transport accidents, nor were there differences between deployed and era veterans for all external causes (SMR = 1.19, 95% CI 0.63–2.25), intentional self-harm (SMR = 1.12, 95% CI 0.39–3.17), or transportation accidents (SMR = 1.19, 95% CI 0.45–3.16).

Secondary Study

In VA's presentation to the committee (Bossarte, 2014), mortality rates of deployed and nondeployed veterans were compared to each other and to the U.S. population. No statistically significant difference was found for all-cause mortality (MRR = 0.98, 95% CI 0.97–1.00) or for all external causes of death (MRR = 1.02, 95% CI 0.99–1.05). However, when external causes of

[15] A summary mortality rate ratio is a summary statistic reflecting the comparison of mortality rates of deployed and nondeployed veterans, whereas a SMR represents a ratio of frequencies (observed deaths in either deployed or nondeployed veterans versus expected number of deaths derived from rates occurring in a reference population, usually the general U.S. population).

death were presented by subcategories of motor vehicle-related, suicide, and homicide, deployed veterans had an increased risk of motor vehicle deaths compared with nondeployed veterans (MRR = 1.09, 95% CI 1.03–1.15). No significant difference in the MRR was found for suicide or homicide among deployed and nondeployed veterans.

The only external cause-specific subcategories using the U.S. population as the reference group were suicide and drivers of motor vehicle crash deaths (Bossarte, 2014). For both the deployed and nondeployed veterans, rates of suicide were statistically significantly lower (SMR deployed and nondeployed = 0.91, 95% CI 0.88–0.95) compared with the U.S. population. The rate of dying as the driver in motor vehicle crashes for deployed veterans was not statistically different from the whole U.S. population (SMR = 0.97, 95% CI 0.91–1.02), but the rate of dying as the driver of motor vehicle crashes for nondeployed veterans was statistically significantly lower compared with the U.S. population (SMR = 0.88, 95% CI 0.83–0.93).

Conclusions

Both the Volume 4 and Volume 8 committees found that the studies of mortality from external causes provided evidence of a modestly higher mortality from all transportation-related causes, specifically motor vehicle crashes (which diminished but persisted), among Gulf War deployed veterans compared with era veterans. These findings are consistent with the new literature reviewed by the Volume 10 committee. Numerous hypotheses have been proposed to account for this increased risk including an increase in risk-taking behaviors following deployment, which may be due to posttraumatic stress or other mental health factors; increased use of alcohol or substances that may increase risk of injury; or possible combat-zone exposures that may lead to ill-defined syndromes that affect decision making, reaction time, or balance (Bell et al., 2001; Gackstetter et al., 2006; Gray and Kang, 2006; Killgore et al., 2008).

Therefore, the Volume 10 committee concludes that there is limited/suggestive evidence of an association between deployment to the Gulf War and an increase in mortality from external causes, primarily motor vehicle accidents, in the early years after deployment. However, after those first few years, there is limited/suggestive evidence of no association between deployment to the Gulf War and external causes of mortality.

Disease-Specific Mortality

As noted above, the committee decided to consider mortality from conditions of specific organ systems (such as cardiovascular and neurologic) or from specific diseases (such as cancer) in this section. The committee notes that mortality data on Gulf War veterans are available for only a few conditions or organ systems.

First, the committee briefly considers the overall rates of disease-specific mortality based on underlying cause of death. In the UK follow-up study (UK Ministry of Defense, 2014), 911 deployed veterans died of disease-related causes compared with 1,073 nondeployed veterans (MRR = 0.88, 95% CI 0.81–0.97; adjusted for age). In the Australian Gulf War Follow Up Study, all disease-specific mortality was not reported. Cancer and cardiovascular disease were the only specific causes of death reported, and are discussed in those sections below. VA's presentation to the committee (Bossarte, 2014) included selected mortality risk rates over a 20-year period (1991–2011) for all disease causes as well as selected subcategories for all deployed and nondeployed U.S. veterans. After adjusting for age, sex, race, branch of service, and unit

component, deployed veterans had a statistically significantly lower rate of death from all disease-related causes compared with nondeployed veterans (MRR = 0.96, 95% CI 0.94–0.98).

Cancer

Summary of Volumes 4 and 8

Cancer mortality in Volumes 4 and 8 focused on brain cancers, although all other cancers were included if data were available. Two primary studies of cancer mortality were reviewed in Volume 4 and one additional primary study in Volume 8. An association of brain-cancer mortality with possible nerve-agent exposure (based on the 2000 DoD exposure model for the Khamisiyah munitions demolition) was observed in one study discussed in Volume 4 (RR = 1.94, 95% CI 1.12–3.34; adjusted for age at entry to follow-up, race, sex, rank, and unit component) (Bullman et al., 2005). The increased relative risk of dying from brain cancer in veterans exposed to 2 days or more at Khamisiyah versus unexposed deployed veterans was further supported after an additional 4 years of follow-up (MRR = 2.71, 95% CI 1.25–5.87; adjusted for sex, race, type of unit, and age) (Barth et al., 2009). Bullman et al. (2005) also assessed the risk of brain cancer mortality from modeled exposure to smoke from the oil-well fires. They found no statistically significant increase in brain cancer death, however, an association of brain cancer death with exposure to smoke from oil-well fires was seen at the later follow-up (MRR = 1.81, 95% CI 1.0–3.27) (Barth et al., 2009). Sex-specific rate ratios were presented and no difference in brain cancer deaths was observed between deployed and nondeployed women or men. However, the Volume 8 committee noted that the numbers of cases of brain cancer in veterans who had possibly been exposed to nerve agents was small, and there was little previous evidence of an association between exposure to sarin or organophosphate pesticides and brain cancer. *Therefore, the Volume 8 committee concluded that there was insufficient/inadequate evidence of an association between Gulf War exposures and brain cancer.*

Primary studies that assessed mortality from all types of cancers in Volumes 4 and 8 failed to show an increased risk in deployed versus nondeployed veterans (Kang and Bullman, 2001; Macfarlane et al., 2003, 2005; DASA 2009; Statistics Canada, 2005). Both committees found that, in general, many veterans were still too young for cancer diagnoses, given the maximum follow-up period of about 10 years, and for most cancers the follow-up period after the Gulf War was probably too short to expect the onset of cancer, let alone death from it. Only the UK statistical report (DASA, 2009) had a follow-up period of 16 years and it found no increase in the number of malignant neoplasms in deployed versus nondeployed UK Gulf War veterans. The Volume 8 committee did not reach any conclusions regarding the association between deployment to the Gulf War and mortality from any cancer.

New Literature

Two of the primary studies described above assessed disease-specific mortality in Gulf War veterans: one in UK veterans and one in Australian Gulf War veterans. The statistical report from UK Ministry of Defence (2014) compared disease-specific mortality rates for deployed and nondeployed UK Gulf War veterans from April 1, 1991 through December 31, 2013. The largest contributor of disease-related deaths was neoplasms: 404 neoplasm deaths out of 911 disease-related deaths in deployed veterans and 455 neoplasm deaths out of 1,035 disease-related deaths in nondeployed veterans. Consistent with previous studies (e.g., Bullman et al., 2005; Barth et al., 2009), no statistically significant difference in the number of deaths due to neoplasms was found between the two groups (MRR = 0.89, 95% CI 0.78–1.02; adjusted for age). Neoplasms

were examined by specific sites. The numbers of deaths from malignant neoplasms of the colon and of the bronchus and lung were statistically significantly lower among the deployed veterans than the comparison group (MRR colon = 0.54, 95% CI 0.31–0.96 and MRR lung = 0.60, 95% CI 0.42–0.85). There was no difference in brain cancer mortality (MRR = 0.71, 95% CI 0.46–1.09).

The Australian Gulf War Veterans' Follow Up Health Study (Sim et al., 2015) compared cancer mortality rates between deployed and nondeployed veterans as well as between each veteran cohort and the age-adjusted Australian male population. Among deployed veterans, observed cancer deaths were slightly higher than expected compared with the age-matched Australian male population, but this difference was not statistically significant. The observed number of cancer deaths in the comparison veteran cohort was lower than expected, but also was not statistically different from the Australian male population. The rate of cancer deaths in deployed veterans was not statistically different from the nondeployed veterans (HR = 1.82, 95% CI 0.88–3.74). Because there were fewer than five brain cancer deaths in both the veteran cohorts, further analyses were not performed.

VA's presentation to the committee was considered a secondary study and included mortality rates from all cancers and specifically for lung and brain cancers (Bossarte, 2014). No statistically significant difference was observed between both the deployed and nondeployed veterans with regard to death from cancer (MRR = 0.99, 95% CI 0.95–1.03; adjusted for race, sex, age, rank, branch of service, and unit component). Mortality rates for lung cancer were calculated for each veteran group, but only compared with the U.S. population, not to each other. Because the committee was not presented with additional information including specific model covariates, adjustment weights, or the denominator for the U.S. mortality population used, it was not possible for the committee to calculate even a crude mortality risk ratio comparing lung cancer deaths between the veteran groups. The lung cancer mortality rates for both deployed and nondeployed veterans were statistically significantly lower than that for the general U.S. population (SMR deployed = 0.60, 95% CI 0.57–0.64; SMR nondeployed = 0.59, 95% CI 0.56–0.62).

VA also presented more detailed information on mortality from brain cancer (Bossarte, 2014). Despite using a non-age–adjusted, 50-year span of mortality in the general U.S. population as the referent group, deployed veterans had a statistically significant decreased risk of dying from brain cancer (SMR = 0.88, 95% CI 0.78–0.98); but there was no difference for nondeployed veterans (SMR = 0.93, 95% CI 0.85-1.02). The MRR appeared to show lower risk of brain cancer mortality for deployed veterans compared with nondeployed veterans, but this difference was not statistically significant (MRR = 0.92, 95% CI 0.80–1.07).

As a follow-up to Barth et al. (2009) and Bullman et al. (2005), VA also performed additional modeling using the subset of deployed Army veterans who were considered to be exposed to smoke from oil-well fires and nerve gas at Khamisiyah (based on a DoD model that was found to have serious limitations by GAO (2004)) to estimate whether they were at increased risk of brain cancer (Bossarte, 2014). Relative risk models were adjusted for sex, race, age, and unit type; no statistically significant differences were found for veterans exposed to smoke from oil-well fires at Khamisiyah overall (RR = 1.42, 95% CI 0.93–2.19) or for veterans exposed to two or more days at Khamisiyah (RR = 1.60, 95% CI 0.80–3.20) compared with nonexposed veterans.

Conclusions

Two new primary studies on mortality from cancer in Gulf War veterans were reviewed. Even after following Gulf War deployed and era veterans for 22 years, no statistically significant differences in mortality were found in either the primary or secondary studies, which is consistent with the findings from Volumes 4 and 8. Furthermore, no differences were found between the mortality rates of the two types of cancers—brain and lung—thought to be of greatest concern for Gulf War veterans.

Therefore, the Volume 10 committee concludes that there is insufficient/inadequate evidence of an association between deployment to the Gulf War and mortality from any form of cancer.

Neurologic Conditions

This section covers conditions and disorders related to the central nervous system (those affecting the brain or spinal cord). The neurologic conditions of interest are primarily degenerative, and include MS, ALS, Parkinson's disease, and Alzheimer's disease. Brain cancer is discussed in the section on cancer.

Summary of Volumes 4 and 8

No studies on MS were reviewed in Volume 4. The Volume 8 committee reviewed one primary study (Barth et al., 2009) and one secondary study (Kelsall et al., 2005) on mortality from MS. Barth et al. compared mortality rates from neurologic conditions 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 nondeployed veterans who served concurrently. Records from the VA Beneficiary Identification and Records Locator Subsystem, a database consisting of all veterans eligible for VA benefits, and the Social Security Administration's Death Masterfile were examined. Death certificates and medical records were reviewed by experts who were blinded to deployment status. A total of 19 deaths due to MS were identified; 6 in the deployed group and 13 in the nondeployed group. There was no increased risk for MS mortality (RR = 0.67, 95% CI 0.24–1.85). Although this was a well-designed study, the authors were unlikely to detect an increased risk of MS associated with deployment because MS mortality is likely to be minimal during the first 15 years of the illness.

ALS was the only neurologic condition of interest reviewed in Volume 4. Two primary studies (Coffman et al., 2005; Horner et al., 2003) and one secondary study (Haley, 2003) found that deployed veterans appear to have an increased risk of developing ALS, but these studies measured ALS incidence, not mortality. Several U.S. and UK mortality studies found no excess risk of dying from ALS among Gulf War veterans, but they were limited by short follow-up periods or their applied methods (DASA, 2005; Kang and Bullman, 1996; Macfarlane et al., 2000). In Volume 8, Barth et al. (2009) updated the original Kang and Bullman (1996) mortality study with data through December 2004. Similar to prior mortality studies, Barth et al. did not find any increase in ALS mortality in Gulf War veterans compared with nondeployed veterans (MRR = 0.96, 95% CI 0.56–1.62; adjusted for sex, race, type of unit, and age).

Neither the Volume 4 nor Volume 8 committees were able to identify any studies of dementia or Alzheimer's disease in Gulf War veterans. Barth et al. (2009) compared mortality from Parkinson's disease in deployed versus nondeployed Gulf War veterans. The adjusted MRR for Parkinson's disease in male veterans was 0.71 (95% CI 0.17–2.99; three deaths among

deployed veterans and eight among nondeployed); there were no cases among female veterans in either group.

New Literature

In the primary report from the UK Ministry of Defence (2014), mortality from diseases of the nervous system conditions as a whole were examined, but because there were so few deaths among the deployed veterans (n = 36) and the era veterans (n = 46), mortality for specific neurologic conditions such as MS, ALS, Alzheimer's disease, or Parkinson's disease, was not presented. No statistically significant increased risk of mortality was found for neurologic conditions between deployed and nondeployed veterans (MRR = 0.80, 95% CI 0.52–1.24; adjusted for age).

VA's presentation to the committee (a secondary study) included crude mortality rates and adjusted mortality rate ratios from three specific neurologic conditions: MS, ALS, and Parkinson's disease (Bossarte, 2014). No statistically significant difference was observed between the deployed and nondeployed veterans with regard to death from MS (MRR = 0.85, 95% CI 0.53–1.34), ALS (MRR = 0.97, 95% CI 0.74–1.28), or Parkinson's disease (MRR = 0.64, 95% CI 0.34–1.21). SMRs for MS were calculated for each veteran group compared with the U.S. population and the mortality rates for both deployed and nondeployed veterans were statistically significantly lower than in the general U.S. population (SMR deployed = 0.47, 95% CI 0.32–0.66; SMR nondeployed = 0.48, 95% CI 0.36–0.64).

Conclusions

Relatively few deaths among either Gulf War deployed or era veterans were related to neurologic causes. Consistent with the one primary study on deaths from neurologic diseases reviewed in Volume 8, the new literature also showed few deaths from these causes. In the one secondary study that presented mortality information on conditions of the nervous system, no statistically significant differences were observed between the deployed and nondeployed veterans.

Therefore, the Volume 10 committee concludes that there is insufficient/inadequate evidence of an association between deployment to the Gulf War and mortality from neurologic conditions, specifically multiple sclerosis, Alzheimer's disease, and Parkinson's disease.

The committee also concludes that there is insufficient/inadequate evidence of an association between deployment to the Gulf and mortality from amyotrophic lateral sclerosis, but the committee recognizes this occurs in the context of limited/suggestive evidence of increased ALS incidence among deployed veterans (as discussed in further detail in the Neurologic Conditions section).

Circulatory System Conditions

Summary of Volumes 4 and 8

No studies of mortality from circulatory system conditions were reviewed in Volume 4. The Volume 8 committee reviewed five primary reports on mortality from cardiovascular conditions in Gulf War veterans from the U.S., UK, and Canada (Bullman et al., 2005; DASA 2009; Kang and Bullman 2001; Macfarlane et al., 2005; Statistics Canada 2005). Although each

study adjusted for basic demographics, such as sex, age, race, branch of service, and various other military-related factors, none adjusted for potential lifestyle confounders, such as smoking or alcohol consumption. None of the adjusted MRRs for cardiovascular conditions in deployed versus nondeployed veterans was statistically significant. *Therefore, the Volume 8 committee concluded that there was limited/suggestive evidence of no association between deployment and mortality from cardiovascular disease in the first 10 years after the war.*

New Literature

Two new primary studies assessed mortality from cardiovascular disease. The UK Ministry of Defence mortality report of Gulf War veterans (2014) found no statistically significant differences in deaths since 1991 due to diseases of the circulatory system between deployed and nondeployed veterans (MRR = 0.88, 95% CI 0.75–1.03; adjusted for age). When SMRs for deployed and nondeployed veterans were compared with the age- and gender-adjusted UK population, both groups of veterans had a statistically significant decreased risk of dying from circulatory system diseases (SMR deployed = 0.48, 95% CI 0.43–0.54; SMR nondeployed = 0.53, 95% CI 0.48–0.59).

A total of 16 deaths (5 deployed and 11 nondeployed) from cardiovascular disease were reported in the Australian Gulf War Veterans' Follow Up Health Survey (Sim et al., 2015). The rates of death from these conditions was not statistically different between the cohorts (HR = 0.79, 95% CI 0.27–2.29; adjusted for age, rank, and branch of service). Mortality from cardiovascular conditions was lower in both veteran cohorts compared with the Australian male population, but neither reached statistical significance (SMR deployed = 0.46, 95% CI 0.19–1.11 and SMR nondeployed = 0.63, 95% CI 0.35–1.14). The authors note that the power of this study to detect excess mortality continues to be limited because the veteran cohort "was still quite young at 30 November 2010, with approximately 40% aged between 35–44 years, and the period of follow up is still relatively short for the purpose of detecting disease-related deaths."

VA's presentation to the committee, which was considered to be a secondary study, included mortality rates from circulatory system diseases (Bossarte, 2014). No statistically significant difference was observed between the deployed and nondeployed Gulf War veterans (MRR = 0.98, 95% CI 0.94–1.02; adjusted for race, sex, age, branch of service, and unit component).

Conclusions

Consistent with the findings of mortality from cardiovascular disease presented in Volume 8, the Volume 10 committee also failed to find any statistically significant differences in mortality from these conditions between deployed and nondeployed veterans after 20 or more years of follow-up. However, the committee notes that the models used to compute MRRs for the UK, Australian, and U.S. studies adjusted for some basic demographics, but did not adjust for lifestyle factors, such as smoking or alcohol consumption, that are known potential confounders for cardiovascular conditions.

Therefore, the Volume 10 committee concludes that there is limited/suggestive evidence of no association between deployment and mortality from cardiovascular disease.

Respiratory Conditions

Summary of Volumes 4 and 8

No studies of mortality from respiratory conditions were reviewed in Volume 4. The Volume 8 committee identified three primary studies on mortality from respiratory conditions in Gulf War veterans from the UK and Canada (Macfarlane et al., 2000, 2005; Statistics Canada, 2005). The UK study assessed mortality through March 31, 1999, and found no excess deaths due to conditions of the respiratory system in either deployed or nondeployed veterans (Macfarlane et al., 2000). An update of the same cohort through 2004 (Macfarlane et al., 2005) again found no excess in deaths related to respiratory disease. Bullman et al. (2005) examined cause-specific mortality through December 31, 2000, in deployed U.S. veterans considered to be exposed or not exposed to nerve agents at the Khamisiyah munitions destruction in 1991. No increase in mortality due to respiratory conditions was seen in the exposed veterans (RR = 1.03, 95% CI 0.62–1.72; adjusted for age). Similarly, no increased risk for respiratory disease mortality was observed when the authors divided the exposed group into persons exposed for 1 day only or for 2 days.

Statistics Canada (2005) conducted a mortality follow-up study of Canadian Gulf War veterans and compared them to randomly selected Canadian veterans who were eligible but not deployed to the Gulf War and to the general Canadian population. There were 5,117 members in the deployed cohort and 6,093 members in the nondeployed population. The authors estimated the study power to be 80% to find a 60% increase in total mortality; however, there were insufficient deaths from respiratory disease to make meaningful comparisons between the veteran cohorts or with the general population.

Two secondary respiratory disease mortality studies were considered by the Volume 8 committee. Kang and Bullman (1996) found that through September 1993 Gulf War veterans had a statistically significant decreased risk of death due to respiratory illness (SMR = 0.14, 95% CI 0.07–0.23) compared with the U.S. population, and a slight but statistically insignificant increase when compared with nondeployed veterans. However, there were only 14 respiratory disease-related deaths in both the deployed and nondeployed groups. An updated mortality study of the same cohort through December 31, 1997 (Kang and Bullman, 2001) found no statistically significant differences between the veteran groups for respiratory mortality and both veteran cohorts had statistically significant lower respiratory mortality compared with the general U.S. population. The Volume 8 committee found no statistically significant excess of mortality due to respiratory disease among Gulf War veterans.

New Literature

In a primary study of UK Gulf War veterans, the UK Ministry of Defence (2014) found few deaths due to respiratory diseases (34 of 1,506 total deaths among the deployed veterans and 36 of 1,583 total deaths among the nondeployed veterans). The difference was not statistically significant (MRR = 0.93, 95% CI 0.58–1.49; adjusted for age). Specific types of respiratory system conditions were not presented. Lung and other respiratory system cancers are considered in the Cancer section. Because the number of deaths due to respiratory conditions was few, standardized mortality ratios comparing deployed and nondeployed veterans with the age- and gender-adjusted UK population were not calculated.

VA's presentation to the committee (Bossarte, 2014) included mortality rates for respiratory conditions for both deployed and nondeployed Gulf War veterans. This secondary

study found no statistically significant difference between the two groups (MRR = 0.96, 95% CI 0.86–1.06; adjusted for race, sex, age, branch of service, and unit component).

Conclusions

The new literature reviewed by the Volume 10 committee was consistent with the literature reviewed in Volume 8, where few deaths due to respiratory causes were reported and no evidence of different mortality rates were observed between deployed and nondeployed veterans.

Therefore, the Volume 10 committee concludes that there is limited/suggestive evidence of no association between deployment to the Gulf War and mortality from respiratory disease.

Gastrointestinal System Conditions

Summary of Volumes 4 and 8

No studies of mortality from gastrointestinal conditions were reviewed in Volume 4. The Volume 8 committee reviewed two studies that assessed mortality from gastrointestinal diseases in UK Gulf War veterans. Macfarlane et al. (2005) assessed mortality over a 13-year follow-up period. Based on National Health Service data, Gulf War veterans experienced fewer deaths from gastrointestinal conditions than the era cohort, but after adjusting for age the difference was not statistically significant (MRR = 0.77, 95% CI 0.40–1.46). The UK Defence Analytical Services Agency (DASA, 2009) published summary statistics on causes of deaths in Gulf War deployed and nondeployed veterans through 2007; the age-adjusted MRR for gastrointestinal conditions was 0.71 (95% CI 0.46–1.11).

New Literature

In a primary study, the UK Ministry of Defence (2014) reported 88 deaths in Gulf War deployed veterans and 92 deaths in era veterans that were caused by gastrointestinal conditions other than cancers, since 1991, the difference was not statistically significant (MRR = 0.97, 95% CI 0.73–1.30; adjusted for age). Specific types of gastrointestinal conditions were not presented. Standardized mortality ratios comparing deployed and nondeployed veterans with the age- and gender-adjusted UK population were not calculated.

In a secondary study, VA (Bossarte, 2014) included mortality rates from gastrointestinal conditions for both deployed and era Gulf War veterans. No statistically significant difference was observed between the two groups (MRR = 1.01, 95% CI 0.93–1.11; adjusted for race, sex, age, branch of service, and unit component).

Conclusions

Based on findings from Volume 8 and the new literature, there is no evidence of a statistically significant difference in mortality from gastrointestinal conditions between deployed and era Gulf War veterans.

Therefore, the Volume 10 committee concludes that there is limited/suggestive evidence of no association between deployment to the Gulf War and mortality from gastrointestinal conditions.

Infectious and Parasitic Diseases

Summary of Volumes 4 and 8

The Volume 4 and Volume 8 committees did not review studies of mortality related to or resulting from infectious and parasitic diseases because those outcomes were examined in *Gulf War and Health, Volume 5: Infectious Diseases* (IOM, 2007). Volume 5 characterized the long-term adverse health outcomes associated with infection by the following pathogens: *Brucella* species (spp.), the cause of brucellosis; *Campylobacter* spp., nontyphoidal *Salmonella* spp. and *Shigella* spp., which cause diarrheal disease; *Coxiella burnetii*, the cause of Q fever; *Leishmania* spp., the cause of leishmaniasis; *Mycobacterium tuberculosis*, which causes tuberculosis; *Plasmodium* spp., the cause of malaria; and West Nile virus, the cause of West Nile fever. That report stated, "Among U.S. Gulf War troops, the overall incidence of infectious diseases was low, mostly composed of acute diarrheal and respiratory infections; less than 20 cases each of viscerotropic leishmaniasis and cutaneous leishmaniasis; three cases of Q fever, a case of West Nile fever, and seven cases of malaria (Hyams et al., 1995, 2001)" (IOM, 2007). During Operations Desert Storm and Desert Shield, infectious diseases reportedly caused only one death among U.S. troops—a fatal case of meningococcal meningitis. The Volume 5 committee did not reach any conclusions on the associations between mortality from infection diseases and deployment to the Gulf War. Volume 5 contains a lengthy discussion of the long-term effects of these infectious diseases, when those effects might be evident, and the role of immunizations.

In the two UK studies of Gulf War deployed and era veterans (DASA, 2009; Macfarlane et al., 2005), fewer than 10 deaths in total were reported for this category. Bullman et al. (2005) examined mortality through 2000 from all and specific causes in Gulf War veterans exposed to the nerve-agent plume at Khamisiyah. A total of 29 deaths from infectious and parasitic diseases were reported in the exposed veterans and 56 deaths in the unexposed, but the difference was not statistically significant (MRR = 1.16, 95% CI 0.74–1.82; adjusted for adjusted for age at entry to follow-up, race, sex, rank, and unit component).

New Literature

The primary UK Ministry of Defence mortality report (2014) listed "certain infectious and parasitic diseases," but did not provide additional details on which specific diseases were included. A cumulative total of 20 deaths in this category since 1991 were reported: 11 deaths among the deployed veterans and 9 deaths in the nondeployed veterans. The difference was not statistically significant (MRR = 1.23, 95% CI 0.50–3.01; adjusted for age).

In a secondary study, VA (Bossarte, 2014) included mortality rates from infectious diseases for both Gulf War deployed and era veterans. A total of 728 deaths and 1,196 deaths were reported among the deployed and era cohorts, respectively. The deployed veterans had a statistically significant decreased risk of dying from infectious diseases compared with era veterans (MRR = 0.74, 95% CI 0.67–0.81; adjusted for race, sex, age, branch of service, and unit component).

Conclusions

Few studies have presented mortality from infectious diseases. However, the results have consistently shown no statistically significant differences between deployed and era veterans. The VA presentation (Bossarte, 2014) suggests that the Gulf War deployed veterans are at less risk of developing and dying from infectious or parasitic diseases than nondeployed veterans; however, the committee did not have a category of association to indicate such a relationship.

Therefore, the Volume 10 committee concludes that there is limited/suggestive evidence of no association between deployment to the Gulf War and infectious or parasitic disease-related causes of mortality.

Limitations of Mortality Studies

Veterans deployed to the Persian Gulf region and veterans serving in the armed forces but not deployed may offer reasonably comparable groups for examining many health outcomes, including death, but there are considerations in the conduct and use of mortality studies. A major limitation of the mortality studies discussed in this section is the short follow-up period. In general, more time is required before investigators will be able to assess whether deployed veterans are experiencing increased mortality compared with their nondeployed counterparts, particularly for conditions with established risk factors and long latencies, such as cancer, or conditions that have deteriorating and protracted courses, such as cardiovascular diseases or some neurodegenerative disorders such as Parkinson's disease.

A further limitation to the U.S. and Australian morality studies is their reliance on the National Death Index for each country. Information in these indexes is taken from death certificates which are completed by different types of health professionals with varying levels of expertise in assessing cause of death. For example, in the United States, information in these indexes is taken from death certificates that are completed by coroners, attending physicians, or medical examiners depending on the laws and processes in place to adjudicate deaths, and are generally state or county specific. Furthermore, cause of death is typically determined based on the first listed cause of death or underlying cause of death, and additional contributing causes of death were not taken into account for classification. The most reliable cause of death information is typically provided by medical examiners and those records are less likely to suffer from nondifferential misclassification bias, especially for causes of death that may have links to specific exposures or require knowledge of underlying pathology (IOM, 2003).

Finally, few studies have been published with enough power to assess cause-specific mortality rates among deployed and nondeployed Gulf War veterans from the U.S. or any coalition country (e.g., UK, Canada, Australia). In addition to large cohort studies comparing deployed and nondeployed veterans, nested case-control studies among the deployed may yield efficient and more suitable comparisons between deceased or "sick" veterans (cases) and alive or "non-sick" (controls) veterans.

TABLE 4-24 Causes of Mortality

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Volumes 4 and 8 Primary Studies						
Cancer						
DASA, 2009 (Vol. 8)	Summary statistics of causes of death from April 1, 1991, to December 31, 2007	53,409 UK GWVs vs 53,143 NDVs	Mortality due to malignant neoplasms	GWVs (209 cases) compared to NDVs (228 cases) MRR = 0.97 (95% CI 0.81–1.18) No significant difference in mortality rate was found for any of the specific classes of malignant neoplasm included in the study	Single years of age structure of the Gulf cohort at January 1, 1991	
Statistics Canada, 2005 (Vol. 8)	Retrospective cohort study (cohort based on Goss Gilroy Inc, 1998)	5,117 Canadian GWVs; 6,093 Canadian NDVs, frequency matched for age, sex, and military duty status	Mortality and cancer incidences determined from the CMD and CCD through 1999	Cancer mortality, HR = 0.85 (95% CI 0.38–1.90) Incidence of any cancer (HR = 0.86, 95% CI 0.54–1.39); cancer of the gastrointestinal system (HR = 2.00, 95% CI 0.62–6.12); testicular cancer (HR = 0.76, 95% CI 0.18–3.24); cancer of the lymph nodes (HR = 0.65, 95% CI 0.16–2.62)	Age, rank	Limitations: Small sample; young age of cohort; short follow-up period; no information on other confounding factors.
Macfarlane et al., 2005 (Vol. 8)	Mortality cohort; 13-year follow-up	51,753 UK GWVs and 50,808 NDVs, randomly selected, matched by age, sex, service branch, rank; also fitness for active service in the army and Royal Air Force	Mortality due to malignant neoplasms	GWVs (123 deaths) vs NDVs (130 deaths): MRR = 1.01 (95% CI 0.79–1.30)		Complete and long-term follow-up; cohort of moderate size; potentially other uncontrolled confounders

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Kang and Bullman, 2001 (Vol. 4)	Cohort mortality study; follow-up from 1991 through 1997	621,902 GWVs vs random sample of 746,248 NDVs	Overall cancer mortality ascertained from BIRLS, death certificates, and NDI	Males: GWVs (cases = 477) vs NDVs (cases = 860): RR = 0.90 (95% CI 0.81–1.01) Females: GWVs (cases = 49) vs NDVs (cases = 103): RR = 1.11 (95% CI 0.78–1.57)	Age, race, branch of service, unit component, marital status	Short latency; low age range; mortality ascertained with death certificates
Bullman et al., 2005 (Vol. 4)	Cohort mortality study (population from same source as Kang and Bullman, 1996, 2001)	100,487 U.S. Army GWVs exposed to chemical warfare agents at Khamisiyah; 224,980 nonexposed Army GWVs; exposure determined from the DoD plume model	Brain cancer mortality through December 2000 ascertained from BIRLS and NDI	Exposed (25 cases) vs unexposed (27 cases) RR = 1.94 (95% CI 1.12–3.34); Exposed 1 day: RR = 1.72 (95% CI 0.95–3.10) Exposed 2+ days: RR = 3.26 (95% CI 1.33–7.96)	Age at entry, race, sex, unit component, and rank	9-year follow-up likely too short to examine brain cancer risk (increases with time since exposure); exposure assessment dependent on accuracy of the DoD plume model; multiple comparisons; death certificate diagnosis
Barth et al., 2009 (Vol. 8)	Mortality cohort study, follow-up through 2004 of Bullman et al. (2005)	621,902 U.S. GWVs and 746,248 nondeployed era veterans; 98,406 GWVs exposed to Khamisiyah nerve agents; 123,478 GWVs	Brain cancer mortality	GWVs (144 cases) vs NDVs (228 cases) MRR = 0.90 (95% CI 0.73–1.11) Khamisiyah exposed: MRR = 2.71 (95% CI 1.25–5.87) Oil-well fire smoke exposed: MRR = 1.81 (95% CI 1.00–3.27)	Race, service branch, type of unit, age, marital status, and sex	Similar results after 19 misclassified cancers removed from analysis; see Bullman et al., (2005)

Study	Design	Population	Outcomes	Results	Adjustments	Comments
		exposed to oil-well fire smoke				
Conditions of the Nervous System						
Barth et al., 2009 (Vol. 8)	Mortality cohort study, follow-up through 2004 of same cohort as Kang and Bullman (2001)	621,901 U.S. male GWVs and 746,247 male NDVs	Mortality due to MS (McDonald criteria)	GWVs (6 cases) vs NDVs (13 cases) MRR = 0.67 (95% CI 0.24–1.85)	Race, service branch, type of unit, age, marital status	
Cardiovascular Conditions						
Kang and Bullman, 2001 (Vol. 8)	Cross-sectional, mortality 1991–1997	621,902 GWVs, 746,248 NDVs	Mortality and vital status determined with VA BIRLS database and SSA Master Beneficiary Record database	Men RR = 0.90 (95% CI 0.81–1.01) Women RR = 0.96 (95% CI 0.55–1.69)	Age, race, service branch, type of unit, marital status	Study had good power; limited by relying on death certificates rather than medical records; no adjustment for predeployment health status or confounders
Bullman et al., 2005 (Vol. 8)	Retrospective cohort; follow-up from March, 1991 through 2000	100,487 U.S. Army GWVs exposed to chemical warfare agents at Khamisiyah; 224,980 nonexposed Army GWVs (derived from Kang and Bullman, 2001);	Association of exposure to chemical warfare agents and mortality due to diseases of the circulatory system, determined through BIRLS, SSA; COD data	1.76% exposed vs 1.88% nonexposed RR = 0.89 (95% CI 0.74–1.06)	Age, race, sex, rank, unit component	Possible exposure misclassification, possible bias due to healthy warrior effect

Study	Design	Population	Outcomes	Results	Adjustments	Comments
		exposure determined from the DoD (2000) plume model	from NDI			
Statistics Canada, 2005 (Vol. 8)	Retrospective cohort study (cohort based on Goss Gilroy Inc, 1998)	5,117 Canadian GWVs; 6,093 Canadian NDVs, frequency matched for age, sex, and military duty status	Mortality due to diseases of the circulatory system determined from the CMD and CCD	MRR = 0.49 (95% CI 0.17–1.40)	Age, sex, rank, marital status	Small sample; short follow-up; young age of cohort; no information on smoking
Macfarlane et al., 2005 (Vol. 8)	Cohort; 13-year follow-up	51,753 UK GWVs and 50,808 NDVs, randomly selected, matched by age, sex, service branch, rank; also fitness for active service in the Army and Royal Air Force	Mortality due to diseases of the circulatory system	MRR = 0.87 (95% CI 0.66–1.14)		Complete and long-term follow-up; cohort of moderate size; no control for confounding variables
DASA, 2008 (Vol. 8)	Summary statistics of causes of death from April 1, 1991, to December 31, 2007	53,409 UK GWVs vs 54,143 NDVs	Mortality due to diseases of the circulatory system	MRR = 0.87 (95% CI 0.70–1.07)	Age	Roughly the same cohort as Macfarlane et al., 2005

Study	Design	Population	Outcomes	Results	Adjustments	Comments
Macfarlane et al., 2000, 2005 (Vol. 8)	Cohort study	2000: 53,462 UK GWVs vs 53,450 NDVs 2005: 51,753 UK GWVs and 50,808 NDVs	Mortality (1991–1999/2004) due to diseases of the respiratory system	2000: 3 deaths in GWVs vs 3 deaths in NDVs, MRR = 1.0 (95% CI 0.1–7.5) 2005: 9 deaths in GWVs vs 6 deaths in NDVs, MRR = 1.64 (95% CI 0.58–4.66)	Matching by sex, age, branch, fitness for service	
Bullman et al., 2005 (Vol. 8)	Cohort mortality study; follow-up from March 1991 through 2000	100,487 U.S. Army GWVs exposed to chemical warfare agents at Khamisiyah; 224,980 nonexposed army GWVs; exposure	Association of exposure to chemical warfare agents and respiratory disease mortality, determined through BIRLS, SSA; COD data from NDI	Exposed vs unexposed RR = 1.03 (95% CI 0.62–1.72)	Age, race, sex, rank, unit component	Short duration of follow-up; possible exposure misclassification
External Causes of Mortality						
Kang and Bullman, 1996, 2001 (Vol. 4)	Retrospective cohort, 2.4-year follow-up; Retrospective cohort, approximately 7-year follow-up	695,516 GWVs vs 746,291 NDVs	Mortality 1991–1997; Cox proportional hazards models	Increased deaths from motor vehicle accidents in Kang and Bullman, 1996 (RR = 1.31, 95% CI 1.14–1.49) RRs became nonsignificant in Kang and Bullman, 2001 (RR = 1.17, 95% CI 0.98–1.4) in 1994–1995; Increased HIV deaths in NDVs; no difference in potential nerve gas exposure; no homicide or suicide increase	Sex, age, race, marital status, branch of service, type of unit	Short duration of follow-up; healthy warrior effect may obscure difference
Macfarlane et al., 2000 (Vol. 4)	Cohort study	53,462 UK GWVs vs 53,450 UK NDVs	Mortality 1991–1999	Higher mortality in GWVs from external causes (MRR = 1.18, 95% CI 0.98–1.42); no increase in homicide or suicide	Matching by sex, age, branch, fitness for service	

Study	Design	Population	Outcomes	Results	Adjustments	Comments
DASA, 2005 (Vol. 4)	Summary statistics of causes of death from April 1, 1991, to June 30, 2005	53,409 UK GWVs vs 53,143 UK NDVs	Mortality 1991–June 2005	No increase in mortality except small and nonsignificant increase in transport accidents (SMR = 1.21, 95% CI 0.96–1.51); other external causes of accidental injury (SMR = 1.07, 95% CI 0.74–1.54); higher deaths from external causes disappeared about 10 years after Gulf War	Matching by sex, age, branch	
Lincoln et al., 2006 (Vol. 8)	Retrospective cohort and nested case-control; risk factors for motor vehicle crash fatality (cohort derived from Kang and Bullman, 1996)	1,318 cases of motor vehicle crash mortality (1991–1995) identified from the VA's 1991 Gulf War cohort: 765 deployed GWVs, 553 NDVs; COD, demographic, and military records from DMDC and FARS	Annual motor vehicle mortality rate by risk factor	Higher motor vehicle annual mortality rate in deployed veterans: 23.56 (95% CI 21.9–25.3) for deployed vs 15.87 (95% CI 14.6–17.3) for nondeployed per 100,000		Deployed population possibly associated with greater risk-taking behavior (younger, less educated, not married)
Macfarlane et al., 2005 (Vol. 8)	Cohort; 13-year follow-up (Follow-up of Macfarlane et al., 2000)	51,753 UK GWVs and 50,808 NDVs, randomly selected, matched by age, sex, service branch, rank; also fitness for	Mortality rates	All causes (MRR = 1.03, 95% CI 0.92–1.15); external causes (MRR = 1.19, 95% CI 1.02–1.39); transport accidents (MRR = 1.44, 95% CI 1.13–1.84); intentional self-harm (MRR = 1.04, 95% CI 0.80–1.36) No self-reported Gulf War theater exposure significantly associated		Complete and long-term follow-up; cohort of moderate size; potentially uncontrolled confounders

Study	Design	Population	Outcomes	Results	Adjustments	Comments
		active service in the army and Royal Air Force		with all cause, disease-related, or external mortality		
DASA, 2009 (Vol. 8)	Summary statistics of causes of death from April 1, 1991, to December 31, 2007	53,409 UK GWVs vs 54,143 NDVs)	Mortality data, causes of death classified based on ICD-10	All external cause mortality (MRR = 1.09, 95% CI 0.95–1.25) No significant difference in mortality rate was found for any of the specific external causes of mortality included in the study	Single years of age structure of the gulf cohort at January 1, 1991	
Statistics Canada, 2005 (Vol. 8)	Retrospective cohort (cohort based on Goss Gilroy Inc, 1998)	5,117 Canadian GWVs; 6,093 Canadian NDVs, frequency matched for age, sex, and military duty status	Mortality and cancer incidences determined from the CMD and CCD, 1991–1999	All external causes (OR = 1.53, 95% CI 0.82–2.86); motor vehicle crash (OR = 0.74, 95% CI 0.18–3.11); air/space crash (OR = 5.50, 95% CI 1.16–26.0); suicide (OR = 1.17, 95% CI 0.46–2.95)	Age, rank	
Bullman et al., 2005 (Vol. 8)	Cohort mortality study; follow-up from March 1991 through 2000 (population from same source as Kang and Bullman, 1996, 2001)	100,487 U.S. Army GWVs exposed to chemical warfare agents at Khamisiyah; 224,980 nonexposed army GWVs; exposure determined from the DoD plume model (Rostker, 2000)	Association of exposure to chemical warfare agents and mortality, determined through BIRLS, SSA; COD data from NDI	Exposed vs unexposed Any external cause: relative risk = 1.01 (95% CI 0.92–1.10) Suicide: relative risk = 1.05 (95% CI 0.88–1.25) Motor vehicle fatalities: relative risk = 1.00 (95% CI 0.86–1.17)	Age, race, sex, rank, unit component	Short duration of follow-up; possible exposure misclassification

Volume 10 Primary Studies

Study	Design	Population	Outcomes	Results	Adjustments	Comments
UK Ministry of Defence, 2014	Annual mortality report using national death data reported between April 1, 1991, and Dec. 31, 2013 (reported as of Feb. 1, 2014)	All 53,409 UK GWVs and 53,143 UK NDVs 1,506 deaths among GWVs; 1,627 deaths among NDVs	External cause and disease-related mortality	Number of deaths in GWVs vs NDVs All causes: 1,506 vs 1,583 (RR = 0.95, 95% CI 0.88–1.02); Disease related: 999 vs 1,035 (RR = 0.88, 95% CI 0.81–0.97); All cancer: RR = 0.89 (95% CI: 0.78–1.02) Colon cancer: RR = 0.54 (95% CI: 0.31–0.96) Lung cancer: RR = 0.60 (95% CI: 0.42–0.85) Brain cancer: RR = 0.71 (95%CI: 0.46–1.09). Neurologic diseases: MRR = 0.80 (95% CI: 0.52–1.24) Circulatory system diseases: MRR = 0.88 (95% CI 0.75–1.03). Respiratory diseases: MRR = 0.93 (95% CI: 0.58–1.49) Gastrointestinal diseases: MRR = 0.97 (95% CI: 0.73–1.30) Infectious diseases: MRR = 1.23 (95% CI: 0.50–3.01) Comparison with age- and gender-adjusted UK population: GWV SMR = 0.48 (95% CI 0.43–0.54); NDV SMR = 0.53 (95% CI 0.48–0.59) External causes: 539 vs 505 (RR = 1.06, 95% CI 0.94–1.2); all subcauses were nonsignificant Transportation accidents: 213 vs	Age and gender, standardized to the general UK population NDVs are similar to GWVs in age, gender, service, regular/reservist status, and rank	

Study	Design	Population	Outcomes	Results	Adjustments	Comments
				183 (RR = 1.16); Other accidental injury: 94 vs 94 (RR = 0.95); Intentional self-harm: 208 vs 190 (RR = 1.09). Comparing veterans to UK population: SMR deployed = 0.60 (95% CI 0.57–0.63); SMR nondeployed = 0.64 (95% CI 0.61–0.67), Deaths from transportation accidents: SMR deployed = 1.86 (95% CI 1.63–2.13); SMR nondeployed = 1.61 (95% CI 1.39–1.86)		
Sim et al., 2015 (Australian Follow Up Health Study)	Cohort study. Longitudinal health survey conducted in 2011; mortality and cancer registry data obtained from the Australian National Death	All Australian Gulf War veterans, follow-up of 1,871 GWVs and 2,922 NDVs	External cause and disease-related mortality (SMR and HR)	GWVs vs NDVs: 108 deaths (2.3%) total deaths reported All cancer: HR = 1.82 (95% CI 0.88–3.74). Cardiovascular disease HR = 0.79 (95% CI 0.27–2.29) No statistically significant differences were found between GWVs and NDVs for all external causes (SMR = 1.19, 95% CI 0.63–2.25), intentional self-harm (SMR = 1.12, 95% CI 0.39–3.17), and transportation accidents (SMR = 1.19, 95% CI 0.45–3.16) Comparing to general male Australian population:	Hazard ratios adjusted for branch of service, rank, and age group as of August 1990	No female deaths identified thus females were excluded from analyses Because of so few deaths, categories of mortality were limited to all cause, overall external causes, intentional self-harm, transport accidents, cancer, and cardiovascular disease

Study	Design	Population	Outcomes	Results	Adjustments	Comments
				All-cause mortality GWV SMR = 0.77 (95% CI 0.58–1.02) NDV SMR = 0.59 (95% CI 0.45–0.76) All external causes GWV SMR = 0.70 (95% CI 0.43–1.13) NDV SMR = 0.61 (95% CI 0.41–0.92) No differences between GWVs or NDVs and the Australian male population were found for intentional self-harm or transport accidents Cardiovascular diseases: GWV SMR = 0.46 (95% CI 0.19–1.11) NDV SMR = 0.63 (95% CI 0.35–1.14)		
Knapik et al., 2009	Systematic review	Persian Gulf or Vietnam veterans N = 20 studies (5 pertain to GWVs)	Meta-analysis of cause of death based on ICD-9 codes	Injury-related SMRR = 1.26 (95% CI 1.16–1.37) in GWVs vs era after 3 to 8 years of follow-up and was associated with motor vehicle accidents (SMRR = 1.39, 95% CI 1.22–1.60) Excess mortality decreased with time after deployment except mortality rates for all external causes and motor vehicle events, which remained significantly higher among GWVs compared with NDVs (external causes SMRR = 1.09, 95% CI 1.04–		Systematic review; no new data.

Study	Design	Population	Outcomes	Results	Adjustments	Comments
				1.14; and motor vehicle SMRR = 1.29, 95% CI 1.18–1.40) No statistically significant difference between GWVs and NDVs was found for suicide or homicide		

NOTE: BIRLS = Beneficiary Identification Records Locator System; CCD = Canadian Cancer Database; CI = confidence interval; CMD = Canadian Mortality Database; COD = Cause of Death; DMDC = Defense Manpower Data Center; DoD = Department of Defense; FARS = Fatality Analysis Reporting System; GW = Gulf War; GWV = Gulf War veteran; HIV = human immunodeficiency virus; HR = hazard ratio; ICD = International Classification of Diseases; MRR = mortality rate ratio; MS = Multiple sclerosis; NDI = National Death Index; NDV = nondeployed veteran; OR = odds ratio; RR = risk ratio; SMR = standardized mortality ratio; SMRR = summary mortality rate ratio; SSA = Social Security Administration; U.S.= United States; UK = United Kingdom; VA = Department of Veterans Affairs.

HEALTH CONDITIONS RELATED TO DEPLETED URANIUM EXPOSURE

A small group of U.S. Gulf War veterans who were exposed to DU have been regularly assessed at the Baltimore VA Medical Center since 1993. Most of the veterans experienced inhalation exposure to DU from cleanup operations, fires, or contaminated tanks and munitions, but some continue to have embedded shrapnel in their bodies from friendly fire incidents. Because surgical morbidity precludes further removal of the embedded DU fragments, surveillance of DU toxicity resulting from the chronic, systemic exposure to DU from embedded fragments has been conducted to medically manage any adverse effects. Additionally, there is concern about DU exposure because it has been shown to be carcinogenic in animals (IOM, 2000, 2008a; NRC, 2008). DU is the only Gulf War biomarker of exposure that can be directly monitored in the urine of exposed veterans.

Although up to 80 DU-exposed Gulf War veterans have been evaluated at least once in this cohort over time, at any single time point, only a small subset of individuals are assessed (McDiarmid et al., 2013). Over the years additional members have been added to the cohort. This small group of Gulf War veterans exposed to DU has been followed biennially for 20 years to identify uranium-related changes in health; findings from these cross-sectional assessments have been routinely published (McDiarmid et al., 2001, 2004, 2006, 2007a,b, 2009, 2011a, 2013, 2015). Veterans were categorized as low exposure (current urinary U concentrations < 0.1 μg U/g creatinine) or high exposure (current urinary U concentrations ≥ 0.1 μg U/g creatinine) (McDiarmid et al., 2000). Comparisons are made based on low versus high DU exposure (Hines et al., 2013) or in some cases small groups of unexposed patients (Shvartsbeyn et al., 2011). Typically, about 35 members undergo clinical evaluation at each follow-up session with about 17–18 veterans in each exposure group (McDiarmid et al., 2009, 2011a). Thus, comparisons are based on small numbers.

Investigators have collected a wide range of data including history, clinical laboratory values, urinary uranium measurement, and psychiatric and neurocognitive assessment biennially. The assessments, conducted over 3 days, include a medical examination; blood and urine samples to assess markers of tubular kidney damage (kidney injury marker-1, neutrophil gelatinase-associated lipocalin, and interleukin-18), renal and bone metabolism, hematological markers, and neuroendocrine markers, and lymphocyte response; pulmonary function testing; radiological exams to detect soft tissue reaction to foreign bodies; and tests of neurocognitive performance (McDiarmid et al., 2013). Results have been described by both Volumes 4 and 8 for each assessed health outcome. Some publications focus on particular assessments, such as biomarkers of genotoxicity (McDiarmid et al., 2011b, Albertini et al., 2015), pulmonary effects in registrants with inhalation exposure (Hines et al., 2013), and skin reactivity (Shiu et al., 2015; Shvartsbeyn et al., 2011).

In general, findings have focused on the radioactive and heavy metal toxicity of DU, although adverse DU-related health effects have not been reported (McDiarmid et al., 2013). At the 16- and 18-year follow-up assessments, there were virtually no statistically significant differences between the high exposure and low exposure groups of veterans for any of the clinical or laboratory parameters measured including:

- endocrine function (i.e., blood glucose, insulin levels, serum concentrations of free thyroxine and thyroid-stimulating hormone as measures of thyroid function, serum follicle-stimulating

hormone, lutenizing hormone, prolactin, and total testosterone) (McDiarmid et al., 2000, 2001, 2004, 2006, 2007a,b, 2009, 2011a);

- blood parameters (i.e., mean number of cells with micronuclei and total number of micronuclei per 2,000 cells; and for frequencies of cells with translocated chromosomes, dicentrics, acentric fragments, color junctions, and abnormal cells) for which all values were in the normal range (Bahmutsky et al., 2011, 2013; McDiarmid et al., 2011b);
- prevalence of cardiovascular disease (McDiarmid et al., 2011a);
- self-reported respiratory symptoms, mean pulmonary function values, and low dose computed tomography or positron emission tomography imaging for chest abnormalities (Hines et al., 2013);
- urinary tract or kidney metabolism (McDiarmid et al., 2011a); and
- semen parameters (McDiarmid et al., 2000, 2001, 2004, 2007a,b, 2009).

Even though no health condition has been consistently observed, urinary concentrations of DU continue to be high, but stable, more than 20 years later. Because tissue concentrations will accrue with continued mobilization of embedded DU, health effects may still be expected to occur and thus, these veterans will continue to be monitored (McDiarmid et al., 2015).

As a part of the surveillance program for Gulf War veterans exposed to DU, skin reactivity to uranium was examined in 40 deployed Gulf War veterans and 46 controls (patients with no known occupational exposure to DU seen at University of Maryland Dermatology Clinic for evaluation of contact dermatitis) who completed a clinical assessment between April–June 2009) (Shvartsbeyn et al., 2011). Patch testing was conducted with an extended metals panel and uranyl acetate in three concentrations (0.25%, 2.5%, and 25%). No patch test allergic reactions to uranyl acetate (0.25%, 2.5% or 25%) were observed in either the high or the low exposure group, but there were more irritant reactions with 25% uranyl acetate than lower concentrations in both groups. The authors concluded that dermatitis observed in deployed veterans is unrelated to their DU exposure. However, it should be noted that the deployed and control groups differed significantly: 74% of controls were female whereas all of the deployed veterans were male. Shiu et al. (2015) assessed the 35 veterans in the 2013 cohort for dermatologic findings. Fragment retainment and related scarring was significantly increased ($p = 0.002$) in veterans exposed to high levels of DU (n = 23) compared with the low exposure group (n = 11); other dermatologic findings such as dermatitis and hypertrophic scarring were also increased in the high exposure group but not significantly so.

Conclusions

The Volume 10 committee finds that there is little evidence of adverse health effects from DU in this group of exposed veterans. However, because of the carcinogenic potential of DU, this group of veterans should continue to be followed to determine any long-term adverse health conditions that may occur in the future.

5

ANIMAL STUDIES

Studies of laboratory animals and other nonhuman systems are essential to understanding possible health effects when experimental research in humans is not ethically or practically possible (NRC, 1991). Animal studies can be used to characterize absorption, distribution, metabolism, elimination, and excretion of chemicals, and they may examine acute (short-term) or chronic (long-term) exposures. Such studies permit a potentially toxic agent to be introduced under controlled conditions (with respect to dose, duration, and route of exposure) to probe effects on many body systems.

Although, animal models are not always ideal replicates of human conditions, there are sufficient similarities between human and animal responses to many toxicants such that animal models can be used to examine mechanistic hypotheses, that is, how the toxic agent exerts its deleterious effects at the cellular and molecular levels. Mechanism-of-action (or mechanistic) studies encompass a range of laboratory approaches with whole animals and with in-vitro systems using tissues or cells from humans or animals. Animal studies can be a valuable complement to human studies of genetic susceptibility or other biomarkers and they can facilitate the study of chemical mixtures and their potential interactions. If the animal models are successful they may be used to evaluate potential therapeutic strategies and interventions.

Early volumes in the *Gulf War and Health* series described animal toxicology studies that focused on the association between exposure to a specific toxicant (e.g., sarin, solvents, combustion products, depleted uranium [DU]) and the health outcomes that may result from that exposure. Among the exposures that have been assessed in animal models are vaccines, pyridostigmine bromide (PB), DU, pesticides, sarin, and stress; the exposures have been assessed individually and as mixtures. Volumes 4 and 8 of the *Gulf War and Health* series were concerned only with associations between being deployed to the Persian Gulf region during the war and the prevalence of health outcomes in deployed versus nondeployed veterans; the two volumes did not examine specific toxicant exposures and thus animal studies were not considered in them.

Based on the premise that different populations of Gulf War veterans inevitably experienced multiple and variable chemical exposures, in this chapter, the committee focuses its review on animal toxicology studies that used multiple exposures which were generally considered to be relevant to those exposures that veterans might have experienced in theater. Thus, studies examining single chemical exposures are not considered here. Because such a review has not been previously conducted by a Gulf War and Health committee, no publication date limits were applied to the literature search for animal studies (see Chapter 2).

ANIMAL MODELS OF GULF WAR ILLNESS

A substantial body of research has been conducted in animal models to determine whether a relationship exists between chemical exposures experienced by veterans during the Gulf War and manifestations of Gulf War illness and other health conditions. Animal models have been used to determine whether the symptoms observed in veterans with Gulf War illness can be reproduced in animals by chemical and vaccine exposures, and if so, what mechanistic underpinnings could contribute to the observed effects. However, it is difficult to design animal models to study Gulf War illness because the types and extent of exposures are unknown and the symptoms of Gulf War illness are diverse.

Neuropathological studies have examined hypotheses that Gulf War-related symptoms are based on the ability of toxicants to increase permeability of the blood-brain barrier, particularly under stressful conditions, and thereby alter brain function, mainly metabolism and histopathology, to produce the symptoms of Gulf War illness. Neurobehavioral approaches have been used to examine whether exposed animals have symptoms that mimic the memory and motor function symptoms of veterans, and whether the symptoms could reflect changes in brain metabolism or histopathology. In addition, some animal studies have examined potential effects of Gulf War toxicants on the reproductive system, the musculoskeletal system, and the immune system as veterans have complained of adverse health effects related to those systems.

There are some challenges in the interpretation of animal study data for the purposes of elucidating Gulf War illness. For example, with the exception of fatigue, symptoms such as headache, and muscle and joint pain, as reported by veterans are difficult to study with standard tests in animals (OTA, 1990). In carrying out its charge, the committee used animal studies to determine whether they provided support for health findings from epidemiologic studies in Gulf War veterans.

This chapter describes studies using the multiple exposures that were reported by veterans during the Gulf War and the effects of those exposures on the brain, and the reproductive, musculoskeletal, and immune systems, as well as behavior and pain. Table 5-1, at the end of this chapter, provides a brief overview of the species, exposures, and main results for each study described in the following sections.

BLOOD–BRAIN BARRIER PERMEABILITY, BRAIN HISTOPATHOLOGY, AND BRAIN METABOLISM AND FUNCTION

Blood–Brain Barrier Integrity

Several investigators have hypothesized that alterations in the blood–brain barrier may be caused by exposure to cholinesterase inhibitors such as the insecticides used to treat the military uniforms, the nerve agent prophylactic PB, and possibly sarin, and that such alterations could be enhanced by the stress of deployment (Abdel-Rahman et al. 2002, 2004; Amourette et al., 2009; Friedman et al., 1996; Grauer et al., 2000; Kant et al., 2001; Lallement et al., 1998; Shaikh et al., 2003; Shaikh and Pope 2003; Sinton et al., 2000; Song et al., 2002, 2004; Tian et al., 2002). Normally the quaternary ammonium structure of PB reduces its ability to enter the brain, precluding its effects on the central nervous system (CNS).

Friedman et al. (1996) found that exposing mice to PB accompanied by an inescapable forced swim stress protocol reduced the dose of PB required to produce a 50% inhibition in brain acetylcholinesterase activity to less than one-hundredth of the usual dose, thus supporting the proposed hypotheses. However, numerous subsequent studies using different species (e.g., rats, mice, and guinea pigs) and multiple different stress paradigms have not replicated those initial findings. Rats exposed to pole climbing avoidance stress plus tritiated PB to assess its blood–brain barrier permeability, showed no radioactivity in brain micropunches and cryosections (Amourette et al., 2009). The authors concluded that although PB induced effects on the CNS (based on earlier studies), these effects did not seem to be mediated by a central passage of PB linked to increased permeability of the blood brain barrier caused by stress. Shaikh et al. (2003) and Shaikh and Pope (2003) also found no evidence that stress (forced running) in combination with paraoxon exposure (an organophospshate insecticide that inhibits acetylcholinesterase) enhanced PB uptake into brain in rats. Song et al. (2004, 2002) reported that restraint stress failed to affect uptake of PB into the brain; treatment with paraoxon did compromise the blood–brain barrier, but only in young rats. Tian et al. (2002) reported that neither forced running nor forced swimming had any effect on PB toxicity, PB uptake into brain, or PB-induced brain cholinesterase inhibition in rats. Kant et al. (2001) reported that rats exposed to PB and given foot shock stress did not show enhanced stress effects on performance or in levels of stress hormones, nor did stress enhance the passage of PB into the brain. Furthermore, in three other studies, stress actually mitigated or even precluded uptake of PB into the brains of mice, guinea pigs, and rats (Grauer et al., 2000; Lallement et al., 1998; Sinton et al., 2000).

In contrast, Abdel-Rahman et al. (2002) combined 28-days of restraint stress in rats with dermal exposure to PB, DEET, or permethrin, either individually or as a mixture of the three chemicals. The combination of chemicals, but not any chemical or stress alone, disrupted blood–brain barrier integrity and produced neuronal death in the cingulate cortex, dentate gyrus, thalamus, and hypothalamus, but not in other regions of the brain. In a later study by this group (Abdel-Rahman et al., 2004), rats exposed to both stress and the chemicals exhibited decreased brain acetylcholinesterase in the midbrain, brainstem, and cerebellum and decreased m2 muscarinic acetylcholine receptor ligand binding in the midbrain and the cerebellum, areas of the brain where no disruption of the blood–brain barrier was observed. The authors suggested that combined stress and the three specific chemicals can damage the cerebral cortex, hippocampus, and cerebellum even in the absence of apparent blood–brain barrier damage.

Brain Metabolism and Histopathology

Multiple aspects of brain metabolism and associated histopathology have also been studied. Scremin et al. (2005) sought to determine if the exposure of veterans to PB as a protective agent would enhance the response to sarin, and lead to delayed behavioral dysfunction, that is, whether induced neurobehavioral dysfunction outlasted effects on inhibition of cholinesterase. Sprague Dawley rats were exposed to low (subsymptomatic) doses of sarin, with or without PB, for 3 weeks with observations of neurobehavioral symptoms as well as brain metabolism, cerebral blood flow, glucose utilization, heart rate, and locomotor activity carried out at 2, 4, and 16 weeks after exposure. Early changes observed at 2 and 4 weeks postexposure included increased regional cerebral blood flow, a finding consistent with known vascular effects of cholinergic agonists. The results indicate that PB protected against some changes seen in the rats exposed to sarin alone. No symptoms, including any changes in regional cerebral blood flood and glucose metabolism, were present in the animals at 16 weeks postexposure. Thus these

studies do not support the hypothesis that delayed symptoms observed in Gulf War illness could be caused by exposure to PB.

A potential synergism of these chemical exposures was subsequently tested by Buchholz et al. (1997), using lower doses in adult Sprague Dawley rats. CNS uptake of C^{14}-labeled permethrin in rats that had received a very high dose of PB (7.75 mg/kg) for 10 days was decreased by 30%, while blood levels of permethrin were not altered by PB treatment. The authors concluded that these results were inconsistent with the hypothesized synergy of such compounds in Gulf War illness. Kant et al. (2001) exposed rats to PB alone or in combination with stress (foot shock) and observed that PB decreased blood acetylcholinesterase by half, but had no effect on cortical brain acetylcholinesterase. PB did not further modify blood corticosterone levels elevated by stress. Thus, PB did not exacerbate the effects of stress on either performance measures or on levels of stress hormones.

A mouse model of Gulf War illness was used to study effects on phospholipid metabolism following coadministration of 2 mg/kg PB and 200 mg/kg permethrin intraperitoneal for 10 days followed by up to a 150-day observation period (Abdullah et al., 2011). The doses used were equal to the LD_{50} (lethal dose for 50% of sample cells) for both compounds: the permethrin dose calculated as the highest expected dose of permethrin expected for Gulf War veterans. No effects were observed at 8 days postexposure, but chronic effects, including cognitive impairment and anxiety, as well as increased astrogliosis in the cortex but not the hippocampus, were observed at 150 days; there was no evidence of microgliosis or neuronal loss. Exploratory brain proteomic analysis found alterations in proteins associated with lipid metabolism and molecular transport in the brain, along with endocrine and immune system metabolic changes. In conjunction with the observations of cortical astrogliosis, the findings suggest a persistent and residual adverse effect on the immune system.

In further experiments by the same group, mice exposed to 1.3 mg/kg/day PB orally, plus 0.13 mg/kg/day permethrin and 40 mg/kg/day DEET dermally, and restraint stress for 28 days (Abdullah, et al., 2012) were reported to exhibit sensorimotor deficits, anxiety, and increased astrocytosis in the cerebral cortex, but no histopathological consequences in the hippocampus, nor any increase in microgliosis. Brain phosphatidyl choline (PC) and sphingomyelin content were increased, with the increase in PC containing monounsaturated fatty acids being higher than PC with saturated and polyunsaturated fatty acids. The authors interpreted the lipid changes as suggestive of alterations in peroxisomal pathways and stearoyl-CoA desaturase activity that might relate to neurobehavioral and neuropathological symptoms following exposure to Gulf War agents. In further study, it was hypothesized that PB and permethrin would modulate the concentration of PC and sphingomyelin, which are reservoirs required for acetylcholine synthesis, and that this modulation would persist at the chronic (150 days) time point (Abdullah, et al., 2013). PC and sphingomyelin were elevated in brains of exposed mice at 150 days after a 10-day exposure. Lysoplatelet-activating factors, which are products of PC, were decreased. Catalase expression (a marker for peroxisomes) was increased in exposed mice. The authors state that these results are similarly suggestive of peroxisomal and lysosomal dysfunction in the mouse brains at chronic time points postexposure.

Husain and Somani (2004) examined exposure to sarin, PB, and PB plus sarin, each with or without exercise, in mice. Exercise was carried out daily for 10 weeks on a treadmill. Daily sarin and PB dosing was administered during the 5th and 6th week only. Biochemical effects were only assayed at 1 day following the 10-week exposures. The exposures, regardless of exercise, significantly lowered butyrylcholinesterase, acetylcholinesterase, and neurotoxic

esterase in plasma, platelets, and nerves, as well as the spinal cord, striatum, and cortex. While the authors concluded that exercise enhanced the adverse effects of Gulf War chemical exposures in mice, the effects observed were minimal and not likely to have biological significance.

DEET (40 mg/kg) or permethrin (0.13 mg/kg) or the combination in 70% ethanol was applied daily to adult male rats for 60 days (Abdel-Rahman et al., 2001). All three conditions produced diffuse neuronal cell death in the cerebral cortex, hippocampus, and cerebellum.

Exposure to chlorpyrifos alone or to a combination of PB, permethrin, and chlorpyrifos for 10 days in adult mice both produced pathological changes in hippocampal, cortical, and amygdalar morphometry (Ojo et al., 2014), including an impairment of synaptic integrity in the hippocampus and altered neuronal differentiation in the dentate gyrus at 3 days postexposure. Both exposures also increased astrocytic glial fibrillary acidic protein immunoreactivity in the piriform cortex, motor cortex, and basolateral amygdala, and were accompanied by an increase in acetylcholine levels in the brain. The study purported to show early changes due to Gulf War agents, but it did not examine the persistence of these effects.

The hypothesis that stress-induced corticosteroids would prime the CNS to produce a robust proinflammatory response to neurotoxicants and lead to systemic inflammation was tested in male mice. In a 17-day exposure period, the mice were treated with PB/DEET (14 days), corticosterone (CORT; 7–17 days), and 1 day (day 15) of di-isopropyl fluorophosphate (DFP), a sarin surrogate (O'Callaghan et al., 2015). The level of CORT used is known to be immunosuppressive; the weights of the thymus and spleens of all mice receiving CORT were reduced 20%. DFP caused neuroinflammation throughout the brain in a manner similar to that caused by sarin, with increased expression of multiple proinflammatory mediators. CORT caused a marked exacerbation of the neuroinflammatory effect of DFP. The combination of PB and DEET did not enhance the DFP-induced neuroinflammation with or without CORT. There was no effect of DFP, with or without CORT, on neurodegeneration, astrogliosis, or microglial activation in the frontal cortex, hippocampus, striatum, or hypothalamus.

Brain Function

PB, permethrin, and DEET exposures combined with restraint stress in rats for 4 weeks reduced numbers of parvalbumin-expressing GABAergic interneurons in some portions of the hippocampus (Megahed et al., 2015). Rats also showed diminished hippocampal neurogenesis at 3 months postexposure. Unfortunately, the ability to apply this information to human health is limited by the use of only 6 rats per group and a relatively high dose of PB (1.3 mg/kg/day). The hippocampus is critical to executive functions, thus this study suggests that, at relatively high doses, PB exposure in the presence of stress could induce delayed neurotoxicity.

Other Brain Effects

Williams et al. (2006) used marmosets to study the effect of vaccination or PB on sleep activity and brain electroencephalography. The investigators were blinded as to treatment group. There were no long-term changes in brain electrical activity or sleep architecture that could be attributed to the treatments with vaccines or with PB.

Summary of Brain Effects

Inconsistent results on the permeability of the blood–brain barrier and associated effects to certain combinations of toxic exposures, but not others, give weak support for the hypothesis that stress-induced damage to the blood–brain barrier is a cause for symptoms of Gulf War illness. Three studies showed increased permeability (Abdel-Rahman et al., 2002, 2004; Freidman et al., 1996), but 10 studies found no such effect (Amourette et al., 2009; Grauer et al., 2000; Kant et al., 2001; Lallement et al., 1998;Shaikh et al., 2003; Shaikh and Pope, 2003; Sinton et al., 2000; Song et al., 2002, 2004; Tian et al., 2002). One animal study suggested that stress-induced elevations in cortisone can exacerbate the neuroinflammatory effects of acetylcholinesterase inhibitors (O'Callaghan et al., 2015). Furthermore, altered phospholipid metabolism, which may be associated with adverse effects on the immune system and peroxisomal and lysosomal function, might persist long after exposure to chemicals associated with Gulf War illness (Abdullah et al., 2011, 2012, 2013). Loss of parvalbumin-expressing GABAergic interneurons could be associated with cognitive deficits according to one study (Megahed et al., 2015).

BEHAVIORAL EFFECTS

Veterans with Gulf War illness have reported cognitive or executive dysfunctions, in particular, deficits in memory, and the illness has also been associated with increases in mood disorders, including anxiety and depression. Relevant to these conditions, experimental animal models have examined changes in acquisition (learning) behavior, in short-term memory, and behavioral characteristics, albeit with the use of widely varying approaches. Several studies have evaluated the effect of Gulf War-related toxicants and aspects of motor function likely based on numerous reports of fatigue in Gulf War illness.

Executive Function

Learning

In general, only two different paradigms of learning have been examined in response to Gulf War illness-related toxicants. Early studies examined the acquisition of lever press responding of rats employing what was effectively a differential reinforcement of low rate (0 second or 16 second) schedule of reward following either repeated administration of PB alone or in combination with permethrin (van Haaren et al., 1999, 2000). The authors found that PB slowed acquisition of this behavior, an effect that was not produced by permethrin alone, nor did permethrin enhance the effects of PB. There are several difficulties with the interpretation of these studies as PB effects appeared only in a fraction of the exposed group and the results are inconsistent and marginal. Furthermore, the behavioral paradigm was dependent upon the animals making contact with the lever after an autoshaping paradigm. Such effects are highly dependent upon the animal's basal activity levels and thus not necessarily reflective of deficient learning per se; the basal activity levels may have been influenced by the drug. In addition, no information is presented on the extent to which these deficits may have reflected motor, motivational, or sickness-related effects.

More recent studies have used other stressors, such as a water maze or climbing a pole to avoid a shock, to measure learning changes in response to Gulf War-related toxicants. One study

combined PB with stress induced by pole climbing avoidance (Lamproglou et al, 2009); other studies have combined PB, permethrin, DEET, and stress to mirror reported Gulf War exposures (Abdullah et al., 2012, Parihar et al., 2013). While all researchers report that the toxicants produced deficits in learning, alternative interpretations cannot be ruled out for any of the studies. Combined PB and stress (climbing a pole to escape or avoid intermittent shock delivery) resulted in a longer latency (i.e., slower learning) to find the platform in the water maze. However, in these studies, the animals also had reduced body weights, which could have affected their swimming response (swimming is a highly effortful motor response, and the stress activity requires significant physical endurance). In addition, in some cases the statistical analysis failed to incorporate a repeated measures component of testing that makes the day-by-day comparisons across groups questionable; moreover, of the 8 days of testing, only 1 day shows a significant effect (Abdullah et al., 2012). Furthermore, PB can cause hypothermia in rodents, an effect that by itself has been shown to impair water maze learning (e.g., Iivonen et al., 2003).

Of the three studies that have examined combined effects of PB, permethrin, and DEET with stress (immobilization restraint stress) on water maze learning in rats, Abdullah et al. (2012) appears to show suggestive beneficial effects of these treatments, at least in males, in the form of shorter path lengths to the submerged platform. Exposed animals also had potential motor deficits, manifest as shorter latencies to fall from a rotating rod (although this could have been a learned escape response). Using this same combination of toxicants, chronic restraint stress exacerbated the effects of the chemicals on water maze learning (Parihar et al., 2013). The effects, however, were inconsistent, and the absence of a group that received stress alone makes it difficult to conclude such synergism exists. Data on body weights across time (supplementary data) show increased body weights in the chemical-alone group relative to other groups indicating systemic effects of chemical exposure that may have affected motivation to perform and learning capability. Thus, the ability of Gulf War-related toxicants to produce changes in learning has yet to be fully established, given that other potential motor, motivational, or physical factors that might affect learning cannot be ruled out.

Memory

Surprisingly, despite reported complaints from Gulf War veterans, there have been few studies to assess explicit memory deficits. Kant et al. (2001) examined the combined effects of PB and stress on delayed alternation performance, a behavioral paradigm that required rats to alternate responses between two response devices, with an imposed delay between such response opportunities. No effects of PB or its enhancement by stress were found, although the delay used in the study (1 second) was likely too short to tap working memory; longer delays were not examined.

Following combined exposures to PB, DEET, and permethrin alone or in conjunction with restraint stress, no deficits were reported in novel object recognition memory, suggesting no deficits in short-term memory (Parihar et al., 2013). This task first familiarizes animals with two objects in an enclosed environment, after which the animal is removed from the environment for some designated period and one object replaced by a novel object. The time spent with the novel object is typically greater, as the subject "remembers" the other object. However, it was clear in this study that total exploration behavior was severely impaired in the group stressed with a combination of PB, DEET, and permethrin, suggesting potential motor or motivational impairments. These impairments could affect the extent to which this group was actually

familiarized with the two objects in the initial testing session, and this would ultimately compromise the study's ability to measure memory.

A subsequent study by the same group using the same exposures did find a deficit in the novel object recognition index in treated animals (Hattiangady et al., 2014). However, as in the earlier study, the extent of contact with the novel objects and the exploration levels were significantly lower in the treated groups, findings that could suggest inadequate learning or familiarity with the objects in this group to begin with, which by itself would produce the type of deficits in novel object recognition memory that were seen. The authors did, however, observe deficits in another measure of short-term memory (that is, place recognition in the absence of such deficits in total exploration levels). Thus, findings were inconsistent across these studies, making it unclear which toxicants impair memory functions per se and which ones might play a supporting role.

Potential memory deficits in mice treated for 10 days with PB and permethrin were reported using a maze, as were neuropathological changes in the brain (Zakrirova et al., 2015). Symptoms were observed in the short term (11–18 days) and in the long term (5 months) postexposure. No cognitive deficits were observed at the short-term point, but by 5 months memory deficits had emerged as had increased astrogliosis and reduced staining of synaptophysin in the hippocampus and cerebral cortex. The doses were 0.7 mg/kg/day for PB and 200 mg/kg/day for permethrin, but the authors did not attempt to compare them to what would be expected in veterans. Unfortunately, no information on body weight of the animals in response to the treatments was provided.

Considered overall, information on memory-related deficits in response to Gulf War exposures is limited and inconsistent, and requires further data to assess the potential confounding effects of deficits in motor or sensory functions and systemic toxicity. For example, few studies provided information on body weight, which might confound observed effects.

Anxiety and Mood-Related Behaviors

Parihar et al. (2013) examined anxiety-like behavior with a widely used approach—the elevated plus maze. Number of entries into open arms and time spent in open arms were reduced in rats exposed to a combination of PB, DEET, and permethrin, and further reduced when the exposure was combined with restraint stress. These findings are consistent with interpretations of anxiety-like behavior as rats spent more time in the closed areas of the maze.

Several other investigators have measured behavior obtained in an open field, where increased behavior in the periphery of the field compared with behavior in the center of the open field is considered to be an index of anxiety-like behavior. Results have been inconsistent. Hoy et al. (2000b) found increases rather than decreases in time spent by male rats in the central area of the open field in response to PB plus DEET, and to permethrin plus DEET in the immediate 24 hours after a 7-day exposure; a greater time in the center arena was seen in female rats in response to PB plus permethrin following a 7-day exposure. Similarly, mice exposed to PB plus permethrin for 10 days showed a reduction in time spent in the perimeter (i.e., greater time in the center) at day 15 postexposure; however, they spent more time in the perimeter at day 30 postexposure in a study by Abdullah et al. (2011).

Two studies have examined combinations of two or more Gulf War chemicals. Combined exposures of both male and female mice to PB, permethrin, DEET, and restraint stress resulted in more time spent in the perimeter in the 15-minute open field test (Abdullah et al., 2012);

however, the differences tend to be about 5 seconds or less, raising questions about their biological significance. Conversely, Hattiangady et al. (2014) examined the effect of the same exposure combination in a similar test in rats and found no effects on time spent in the central zone.

A potentially interesting approach was taken by Servatius and Beck (2005), who examined the possibility that nonspecific symptoms reported in Gulf War illness could reflect classical conditioning effects generated during military service. This hypothesis stipulates that conditioning of symptom effects of toxicant-related exposures could result from environmental stimuli such as sounds or visual cues that would then become conditioned stimuli. Then when these or very similar sounds or visual cues occurred later, the cues could evoke the symptomatology associated with the chemical toxicants. Specifically, the study demonstrated that treatment with PB led to potentiated auditory startle responses occurring in the presence of odors associated with exposures to the stressor (PB), suggesting that such odors could function as conditioned stimuli eliciting PB-related effects. The study found that in rats olfactory stimuli are more significant than visual stimuli; visual stimuli were less or not effective.

Avoidance and escape responses have been examined in two studies. In this paradigm, a cue is presented that signals pending onset of an aversive stimulus (frequently a shock); a designated response after the cue but prior to the onset of the shock is an avoidance response, whereas an escape is defined as a behavioral response occurring in the presence of the shock. Using this approach, Lamproglou et al. (2009) offered rats an opportunity to either avoid or escape shock presentation by climbing a pole. The number of pole climbing trials declined notably across sessions in the PB plus stress groups relative to the stress only group, suggesting more efficient or beneficial avoidance behavior in the former group. This is because climbing the pole prior to the sound initiating the trials actually decreased the numbers of trials (and hence potential shock exposures). No effects of PB, sarin, or the combination on passive avoidance responding were found in rats over a 16-week observation period (Scremin et al., 2003).

Animal models of depression appear limited to a study by Hattiangady et al. (2014) who found rats exposed to a combination of PB, permethrin, and DEET had a reduction in voluntary wheel running and significantly greater latency to eating following a 24-hour fast. Those findings are reminiscent of anhedonia, and as noted by the authors, consistent with decreased motivational levels and depression-like behavior.

As with learning and memory, the studies to date that have examined animal models of anxiety or mood-related disorders do not support any conclusions about the relationship between these disorders and any specific Gulf War-related toxicants.

Motor Function

Most animal studies have evaluated motor function in terms of locomotor activity (ambulation, rearing) and aspects of motor or sensorimotor function.

Locomotor Activity

Locomotor activity is generally assessed in an open arena where levels of ambulation (horizontal movement or distance) and hind-limb rearing-related behaviors are measured. Hoy et al. (2000a,b) examined the effects of PB, permethrin, and DEET, alone and in combinations. Following acute exposures (Hoy et al., 2000a), reductions in locomotor activity in male rats were seen in response to PB and permethrin combined and for DEET and permethrin combined.

Following 7 days of such exposures, both male and female rats had reduced locomotor speed in response to PB and DEET (Hoy et al., 2000b). An increase in activity levels in males given DEET and permethrin was observed, but no effects were found in response to either chemical alone. Another study of combined PB and permethrin reported a very slight increase in time spent in the perimeter of the open field coupled with a reduction in total distance traveled (i.e., lowered locomotor activity levels) at 30 days postexposure (Abdullah et al., 2011). However, no significant effects on locomotor activity were found after exposure to PB for 7 days with or without stress in another study (Dubovicky et al., 2007). Hattiangady et al. (2014) showed that combined exposures to PB, permethrin, DEET, and stress produced no effects on open field behavior, but markedly reduced levels of voluntary wheel running behavior (a self-reinforcing behavior in rodents) were seen.

Two studies examined the effects of sarin and stress. Sustained measurement of activity beginning 2 days prior to exposure through 1 month postexposure to sarin and mild heat stress found no changes in activity levels (Conn et al., 2002). Conversely, a study of sarin alone or in combination with shaking stress, found a decrease in several measures of locomotor activity (Mach et al., 2008).

Some studies suggest that various Gulf War toxicants could reduce locomotor activity, which may be related to the fatigue reported by veterans with Gulf War illness. However, it is difficult to ascertain what the behavioral mechanism(s) of locomotor alterations are given potential confounding (e.g., environmental distractions), and possible systemic toxicant-related sickness behavior which could also reduce locomotor activity levels. This may be more evident when measured during or immediately after toxicant exposures, although such effects have not been reported and body weight changes in response to chemical exposures in these studies are seldom reported. Such interpretations are less likely to confound delayed measures of behavioral effects. Furthermore, slight differences in the size of the open field and the specific operational definitions of the behaviors being measured can translate into substantial differences in outcomes even when the same toxicant administration protocols are used.

Motor and Sensorimotor Function

Aspects of fine motor and sensorimotor function following exposure to Gulf War toxicants were measured in rats using beam walk, inclined plane, forepaw grip, postural reflexes, limb placing, and orienting to vibrissae touch (Abou-Donia et al., 2001, 2002, 2004). Following exposures to PB, permethrin, and DEET, alone or in combination, for up to 45 days, a complex profile of effects led the authors to suggest that PB alone might increase beam walk latency (time to cross a beam) during the treatment period (Abou-Donia, 2001). A subsequent study administered DEET, or DEET and permethrin, for 60 days with PB for the last 15 days (Abou-Donia et al., 2004). PB alone or in combination with DEET or DEET and permethrin increased beam walking time, impaired incline plane performance, and reduced grip strength. However, these exposures also resulted in reduced body weights that could alter these motor functions as well. Exposure to PB and sarin produced deficits similar to those described above, providng some evidence that combined PB and sarin enhanced motor function deficits (Abou-Donia et al., 2002). It is important to note, however, that the exposures in the last study included high doses of sarin with its associated systemic toxicity, which could also lead to motor deficits.

Based on the available studies, it is not clear that lower levels of Gulf War toxicants that may mirror Gulf War veteran exposures alter fine motor functions in the absence of more overt toxicity.

Summary of Behavioral Effects

The committee finds that it is difficult to arrive at any generalities regarding the behavioral studies discussed in this section for the following reasons:

- The studies frequently do not use the same chemicals, doses, or dosing regimens or the same measurement protocols for effects (e.g., timing).
- The studies often use different behavioral paradigms to measure the specific behavioral activities.
- The relevance of the administered doses to humans is often not evident or the doses are quite high compared with suspected human exposures.
- Interpretation of study findings are often difficult given the lack of important data, such as changes in body weights or signs of motivational deficits, which might influence the animal's ability to perform behavioral tests.
- The potential for toxicant-induced confounders, including sickness behavior and hypothermia, which also affect behavior, are frequently not reported and not considered in the data interpretation.

Given these issues, it is not possible to draw reliable conclusions about the effects of Gulf War toxicants on animal behavior as measured by learning, memory, mood, or motor function.

ORGAN SYSTEM EFFECTS

In addition to brain and behavioral effects, investigators have also reported on other potential effects of Gulf War exposures, including testicular changes, musculoskeletal problems, immune effects, and pain response. Because Gulf War illness has many manifestations and symptoms may include joint and muscle pain, infections, and headaches, among others, the committee also reviewed the few studies that focused on other organ system effects. Testicular changes, as a reproductive system effect, are included because they have been a concern to veterans.

Reproductive System

One study assessing sperm and testicular changes in animals exposed to toxicants meant to mirror Gulf War exposures was identified. Male rats were exposed to PB, DEET, and permethrin with and without restraint stress for 28 days (Abou-Donia et al., 2003). Stress alone did not influence these outcomes. Testes of animals exposed to the chemical combination showed histologic abnormalities including arrested spermatogenesis and seminiferous tubule degeneration, effects enhanced under conditions of stress. The authors further investigated the causal mechanism for the observed toxicity and identified apoptosis due to the increased expression of two apoptosis-promoting proteins in testicular tissue. While this study could suggest that exposures such as those experienced by Gulf War veterans may contribute to sperm abnormalities and male infertility, the findings should be viewed with caution, as the animals in the chemical plus stress group also gained less weight, indicating poorer health overall, which compromises the validity of the findings.

Musculoskeletal System

Studies of Gulf War exposures on musculoskeletal function or injury have been carried out in mice and in marmosets. PB and vaccine exposures such as those experienced by Gulf War veterans had no effects on muscle function in marmosets (Stevens et al., 2006). Three 10-week studies in male mice investigated the skeletal muscle effects of combined exposures to PB and exercise stress (Somani et al., 2000; Jagannathan et al., 2001) and PB and/or sarin and exercise stress (Husain and Somani, 2004). Animals were exercised daily, and treatment groups received PB and/or sarin at weeks 5 and 6; doses of PB and sarin were 1.2 mg/kg PB and 0.01 mg/kg sarin (or 1/20th of the LD_{50}). PB with exercise stress, and PB and sarin with exercise stress reduced respiratory exchange ratios during and for several weeks after treatment; the authors suggest that these changes in muscle respiration with and following exercise may enhance oxidative muscle injury. No data was provided on body weight or other indicators of systemic toxicity. The studies in mice suggest a potential mechanism for muscle injury following combined exposures to chemicals and stress designed to mirror those exposures reported by Gulf War veterans.

Immune System

Studies of Gulf War exposures on immune function have been carried out in mice and in marmosets. Little evidence of impaired immune response was observed in marmosets given PB in combination with vaccines (Griffiths et al., 2006; Hornby et al., 2006). Most immune parameters examined were unaffected in female mice exposed to DEET, PB, or JP-8 (jet fuel), singly or in combination (Peden-Adam et al., 2001). All exposures suppressed immunoglobulin-M responses, but this was not exacerbated with mixture exposure. The highest mixture dose increased CD4+ T helper cells, decreased the CD4/CD8 ratio in spleen, and suppressed delayed-type hypersensitivity. In animals treated with melanoma tumor cells and *Listeria monocytogenes*, susceptibility was not affected (Peden-Adam et al., 2001). As mentioned earlier, lipid metabolism studies in mice exposed to combined PB and permethrin over 10 days suggested an adverse effect on the immune system that lasted long after the exposure (Abdullah et al., 2011).

Pain Response

Nutter et al. (2015) reported a study in which 30 rats were exposed to permethrin, chlorpyrifos, and PB, over 30 or 60 days. The dosages were calculated on the basis of what Gulf War veterans might have experienced and are described as an intensified anticholinesterase exposure protocol relative to earlier studies by this group that did not influence pain behavior (Nutter et al., 2013; Nutter and Cooper, 2014). The exposures did not statistically affect body weight compared with controls. Assessment of pain behavior relied on right hind-limb withdrawal in response to force application as well as activity levels (15-minute test periods in an open field). The study reported increases in resting time in the 30-day treated group for approximately 8 weeks postexposure, and the 60-day treated group exhibited increased resting time and reduced movement for 12 weeks postexposure, which the authors interpret as consistent with a delayed myalgia in rats and which was seen in conjunction with a decline in activity of muscle nociceptor channel activity and protein expression.

CONCLUSIONS

Animal studies have suggested physiological alterations in response to the toxicant exposures that Gulf War veterans might have experienced while deployed. However, animal studies have typically examined isolated symptoms of Gulf War illness rather than the symptom clusters that are reported by veterans. The lack of information on the actual exposures experienced by veterans during the Gulf War has resulted in a multiplicity of animal study designs that provide inconsistent results. Animal studies have not been successful in suggesting a mechanism by which deployment exposures during the Gulf War might lead to Gulf War illness or its many symptoms.

The committee concludes that although the existence of an animal model would be advantageous for identifying and evaluating treatment strategies for Gulf War illness, it cautions that developing such an animal model is not possible given researchers' inability to realistically determine the exposures associated with Gulf War deployment, let alone the frequency, duration, or dose of those exposures, or the effect of multiple exposures.

Table 5-1 Animal Studies on Gulf War Illness and Other Organ System Effects

Study	Exposure	Result
Blood-brain barrier integrity		
Abdel-Rahman et al., 2002 Rats	DEET + PB + permethrin + stress Exposed dermally for 28 days to 11.3 mg/kg/d PB, 40 mg/kg/d DEET, and 0.13 mg/kg/d permethrin individually or as a mixture of the three chemicals, with or without restraint stress	Evidence of increased blood-brain barrier permeability with exposures to mixture of three chemicals plus stress, but not to any one chemical with or without stress; only affected certain regions: cingulate cortex, dentate gyrus, thalamus, and hypothalamus
Abdel-Rahman et al., 2004 Rats	DEET + PB + permethrin + stress Expose dermally for 28 days to 11.3 mg/kg/d PB, 40 mg/kg/d DEET, and 0.3 mg/kg/d permethrin individually or as a mixture of the three chemicals, with and without restraint stress	Stress plus combined exposure to the three chemicals resulted in decreased brain AChE in certain areas of the brain (midbrain, brainstem, cerebellum) and decreased m2 muscarinic acetylcholine receptor binding (midbrain and cerebellum), areas where no disruption of the blood-brain barrier was observed
Amourette et al., 2009 Rats	PB + stress Two 5-day periods of daily exposure to 1.5 mg/kg 3H-PB with and without stress of pole climbing avoidance	No evidence of increased blood-brain barrier permeability to PB with stress
Friedman et al., 1996 Mice	PB + stress Daily ip injections of 0.5 or 1.0 mg/kg of PB with or without stress of two 4-min forced swim sessions.	Evidence of increased blood-brain barrier permeability to PB with stress

Study	Exposure	Result
Grauer et al., 2000 Mice	PB + stress Stress by two 4-min forced swim sessions or 5 min with feet in ice water and then treated with saline, 0.4 mg/kg PB or 0.2 mg/kg physostigmine im or ip	Evidence of decreased blood-brain barrier permeability to PB with stress
Kant et al., 2001 Rats	PB + stress Treated with 200 µl of saline, 25 mg/ml PB, or 20 mg/ml physostigmine, administered by osmotic minipump, with and without avoidance/escape stress, or yoked stress	No evidence of increased blood-brain barrier permeability to PB with stress
Lallement et al., 1998 Guinea pigs	PB + stress Exposure to saline or 0.2 mg/kg PB with or without stress: low (24.3–25.9°C for 2 hrs); medium (38.4–39.6°C for 2 hrs); or high (42.6°C for 2 hrs)	Evidence of decreased blood-brain barrier permeability in response to PB with stress
Shaikh et al., 2003 Rats	PB + stress + paraoxon 1: control: DMSO im and saline 2: 10 mg/kg PB 3: 30 mg/kg PB 4: 0.1 mg/kg paraoxon 5: 0.1 mg/kg paraoxon + 10 mg/kg PB 6: 0.1 mg/kg paraoxon + 30 mg/kg PB 60 min forced running after treatment	No evidence of increased blood-brain barrier permeability to PB with stress or paraoxon
Shaikh and Pope, 2003 Rats	PB + paraoxon 1: control, vehicle 2: 10 mg/kg PB 3: 30 mg/kg PB 4: 0.1 mg/kg paraoxon 5: 10 mg/kg PB + 0.1 mg/kg paraoxon 6: 30 mg/kg PB + 0.1 mg/kg paraoxon	No evidence of increased blood-brain barrier permeability to PB with paraoxon
Sinton et al., 2000 Rats	PB + stress Restraint stress or forced swimming (or both), or heat stress, followed by PB (0.5, 1, 2, 3, or 5 mg/kg ip); No stress + PB or physostigmine (0.1, 0.2, 0.5, 1, or 2 mg/kg) or saline.	Evidence of decreased blood-brain barrier permeability to PB with stress
Song et al., 2002 Rats	PB + stress 1: controls: saline and no stress 2: 30mg/kg PB, no stress 3: stress protocol only 4: stress protocol with PB Stress protocols A: restraint tube (90 min) then PB; B: PB then restraint tube (60 min); C: restraint tube (3 hr), then PB, then restraint tube (60 min)	No evidence of increased blood-brain barrier permeability to PB with stress
Song et al., 2004 Rats	PB + paraoxon Treatment: 30 mg/kg PB by gavage 50 min	Paraoxon increased the number of leaky capillaries in the brain of

Study	Exposure	Result
	before 100 µg/kg paraoxon im	young rats but not older rats
Tian et al., 2002 Rats	PB + stress 1: controls, no stress or PB 2: no stress, 30 mg/kg PB 3: stress and saline 4: stress and 30 mg/kg PB Stress: forced run on a treadmill after, before, or before and after PB treatment; or forced swimming before or after PB treatment	No evidence of increased PB toxicity or increased blood-brain barrier permeability to PB with stress
Brain metabolism and histopathology		
Abdel-Rahman et al., 2001 Rats	DEET + permethrin All conditions applied dermally 1: control: 70% ethanol 2: 40 mg/kg DEET in ethanol 3: 0.13 mg/kg permethrin in ethanol 4: DEET + permethrin in ethanol 7 d per week for 60 d	Evidence of diffuse neuronal cell death in cerebral cortex, hippocampus, and cerebellum for all three exposures
Abdullah et al., 2011 Mice	PB + permethrin Single dose of 2 mg/kg PB and 200 mg/kg permethrin in DMSO, or DMSO only, ip for 10 d followed by 115-d observation period	Cognitive impairment and anxiety observed at 115 days as well as astrogliosis in the cortex. No effects at 8 d. No neuronal loss or microgliosis. Changes in proteins associated with lipid metabolism and molecular transport and changes in endocrine and immune associated proteins
Abdullah et al., 2012 Mice	DEET + PB + permethrin + stress Control: water, and topical 70% ethanol Treatment: 1.3 mg/kg PB in water; 0.13 mg/kg permethrin and 40mg/kg DEET in 70% ethanol dermally; and 5min of restraint stress; 28 days. 42-d observation period.	Evidence of astrocytosis in the cerebral cortex and increased lipids (phosphatidyl choline and sphingomyelin) in the brain
Abdullah et al., 2013 Mice	PB + permethrin Single dose of 2 mg/kg PB and/or 200 mg/kg permethrin in DMSO, or DMSO only, ip for 10 days. 150-d observation period.	Evidence of increased phosphatidyl choline and sphingomyelin in the brain and other changes (decreased lysoplatelet activating factors and increased catalase expression) indicating peroxisomal and lysosomal dysfunction
Buchholz et al., 1997 Rats	PB +permethrin 1: PB 7.75mg/kg in food 2: PB +14C-permethrin 4.75µg/kg ip 3: controls, plain food for 10 days.	No evidence of harmful synergistic effect of PB and permethrin on central nervous system
Husain and Somani, 2004 Mice	PB + sarin + stress 1: Controls 2: 0.01mg/kg/d sarin sc for weeks 5 and 6 3: exercise on treadmill daily for 10 weeks	Little evidence that exercise increased the effects of PB or sarin on butyrcholinesterase, AChE, neurotoxic esterase in plasma or

Study	Exposure	Result
	with increasing speed and time 4: sarin + exercise 5: 1.2 mg/kg/d PB orally for weeks 5 and 6 6: PB + exercise 7: PB + sarin 8: PB + sarin + exercise Animals sacrificed 24 hrs after last treatment	brain
Kant et al., 2001 Rats	PB + stress Treated with 200 µl of saline, 25 mg/ml PB, or 20 mg/ml physostigmine administered by osmotic minipump at a rate of 1.5 or 1.2 mg/kg/d, with and without avoidance or escape stress, or yoked stress	No evidence that PB exacerbated the effects of stress. PB decreased blood AChE by half, but had no effect on cortical brain AChE and no effect on blood corticosterone levels elevated by stress
O'Callaghan et al., 2015 Mice	DEET + PB + corticosterone+ DFP 1: PB 3 mg/kg/d sc + DEET 30 mg/kg/d sc for 14 days, 300 mg/L cortisone in drinking water on days 8-15, and DFP on day 15 2: Controls, saline sc	Evidence that cortisone exacerbated the neuroinflammatory effect of DFP
Ojo et al., 2014 Mice	PB + permethrin + chlorpyrifos 1: 5 mg/kg/d chlorpyrifos ip 2: chlorpyrifos + 0.7 mg/kg/d PB + 200 mg/kg/d permethrin, ip 3: control, DMSO ip 10 days	Evidence of pathological changes in hippocampal, cortical, and amygdalar morphometry in both exposure groups at 3 days post exposure, but these early changes did not persist
Scremin et al., 2005 Rats	PB + sarin 1: control, tap water and saline injection 2: 80 mg/L PB in drinking water and saline sc 3: tap water and 62.5 µg/kg sarin sc 3 times/week 4: PB in water and sarin sc For 3 weeks; sacrificed at 2, 4, 16 weeks after treatment	Evidence of effects on brain metabolism at 2 and 4 weeks (increased cerebral blood flow, glucose utilization but not at 16 weeks
Brain Function		
Megahead et al., 2015 Rats	PB + permethrin + DEET + stress controls; treatment: 1.3 mg/kg/d PB in water by oral gavage, 40 mg/kg/d DEET and 0.13 mg/kg/d permethrin dermally, and 5 min/d restraint stress for 4 weeks. 3-month observation period.	Evidence of reduced numbers of parvalbumin and neuropeptide Y expressing interneurons in some parts of hippocampus and diminished hippocampal neurogenesis
Other Brain Effects		
Williams et al., 2006 Marmosets	PB + vaccines 1: vaccinated with 20% of human dose or vehicle in period 1 (first 51 days); 2: 500 µg/kg/d PB by miniosmotic pump or sterile saline 21 months	No evidence of long term effects of vaccination or PB on brain electrical activity or sleep architecture

Study	Exposure	Result
Executive Function		
Abdullah et al., 2012 Mice	DEET + PB + permethrin + stress Control: water, and topical 70% ethanol Treatment: 1.3 mg/kg PB in water; 0.13 mg/kg permethrin and 40 mg/kg DEET dermally; and 5 min of restraint stress; 28 days. 42-d observation period	Evidence of possible beneficial effects of PB in water maze performance but deficits on a rotating rod
Hattiangady et al., 2014 Rats	DEET + PB + peermethrin + stress Treatment group: 40 mg/kg/d DEET dermally + 0.13 mg/kg/d permethrin dermally + 1.3 mg/kg/d PB by gavage + 5 min/d restraint stress; for 4 weeks Testing conducted 3 months after exposure	Evidence that treatment impaired place recognition memory and caused novel object recognition memory dysfunction
Kant et al., 2001 Rats	PB + physostigmine + stress Treated with 200 µl of saline, 25 mg/ml PB, or 20 mg/ml physostigmine administered by osmotic minipump; with and without avoidance or escape stress, or yoked stress	No evidence of effect of PB or physostigmine and stress on working memory
Lamproglou et al., 2009 Rats	PB + stress 1: 1.5mg/kg/d PB in water 2: stress (pole climbing avoidance days 1-12) 3: stress + PB (given 30 min before stress, treatment daily on days 1–5 and 8–12) Testing on days 15–199; sacrifice at day 12 or 199	Evidence of long-term behavioral effects (aggressiveness, impulsiveness, learning dysfunction)
Parihar et al., 2013 Rats	DEET + PB + permethrin + stress 1: control vehicle and handling daily 2: 40 mg/kg/d DEET and 0.13 mg/kg/d permethrin dermally, and 1.3mg/kg/d PB by gavage 3: DEET + PB + permethrin + stress (restraint stress 5min/d) 4: control group 4 weeks	Evidence of increased depressive and anxiety-like behavior and spatial learning and memory dysfunction; and effects of stress on mood and cognitive dysfunction; no evidence of effect on novel object recognition memory, possible effect on exploration behavior in rats exposed to chemicals + stress
Van Haaren et al., 2000 Rats	PB + permethrin 1: controls (water and vehicle) 2: 1.5mg/kg/d PB for 7 d by gavage 3: permethrin (0, 15, or 60 mg/kg) by gavage before session in an operant chamber 4: PB + permethrin	No evidence of behavioral effects of permethrin; evidence of delayed response acquisition in rats treated with PB
Zakirova et al., 2015 Mice	PB + permethrin Treatment: 0.7 mg/kg/d PB and 200 mg/kg/d permethrin ip for 10 days. Testing at 18-d and 5-months postexposure	Evidence of long-term effects on cognition (memory deficits) and neuropathology associated with PB and permethrin
Anxiety and Mood-Related Behaviors		
Abdullah et al., 2011 Mice	PB + permethrin Single dose of 2 mg/kg PB and/or 200 mg/kg Permethrin in DMSO, or DMSO only, ip for	Evidence of decreased anxiety-like behavior at in rats exposed to PB and permethrin at 15 days

Study	Exposure	Result
	10 d. 115-d observation period	postexposure, but increased anxiety-like behavior at 30 days.
Abdullah et al., 2012 Mice	DEET + PB + permethrin + stress Control: water, and topical 70% ethanol Treatment: 1.3 mg/kg PB in water; 0.13 mg/kg permethrin and 40 mg/kg DEET dermally; and 5 min of restraint stress; 28 days. 42-d observation period	Evidence of increased anxiety-like behavior
Hattiangady et al., 2014 Rats	DEET + PB + permethrin + stress Treatment group: 40 mg/kg/d DEET dermally + 0.13 mg/kg/d permethrin dermally + 1.3 mg/kg/d PB by gavage + 5 min/d restraint stress For 4 weeks; testing conducted 3 months after exposure	No evidence of effect on anxiety-like behavior; evidence for depression-type behavior
Hoy et al., 2000b Rats	DEET + PB + permethrin 1: 7.5 mg/kg PB by gavage 2: 200 mg/kg DEET by gavage 3: 60 mg/kg permethrinr ip 4: 3.75 mg/kg PB + 30 mg/kg permethrin 5: 3.75 mg/kg PB + 100 mg/kg DEET 6: 2.5 mg/kg PB + 20 mg/kg permethrin + 67 mg/kg DEET 7: 100 mg/kg DEET + 30 mg/kg permethrin Daily for 7 days; testing conducted 24 hr after last treatment	Evidence of reduced anxiety-like behavior in male rats exposed to PB + DEET and permethrin + DEET and female rats exposed to PB + permethrin
Lamproglou et al., 2009 Rats	PB + stress 1: 1.5 mg/kg/d PB in water 2: stress (pole climbing avoidance days 1-12) 3: stress + PB (given 30 min before stress, treatment daily on days 1–5 and 8–12) Testing on days 15–199	Evidence of beneficial avoidance behavior
Parihar et al., 2013 Rats	DEET + PB + permethrin + stress 1: control vehicle and handling daily 2: 40 mg/kg/d DEET and 0.13 mg/kg/d permethrin dermally, and 1.3 mg/kg/d PB by gavage; 3: DEET + PB + permethrin + stress (restraint stress 5 min/d) 4: control group 4 weeks	Evidence of increased anxiety-like behavior in rats exposed to PB, DEET, permethrin, and stress
Scremin et al., 2003 Rats	PB + sarin 1: PB 80mg/L in drinking water 2: sarin 62.5µg/kg 3 times/week sc 3: PB + sarin 3 weeks; assessed at 2, 4, or 16 weeks after treatment	No evidence of effects of PB or sarin on avoidance behavior at 16 weeks

Study	Exposure	Result
Servatius and Beck, 2005 Rats	PB + neostigmine+ interleukin PB: 0.1 or 1.0 mg/kg ip Neostigmine: 0.016 mg/kg ip Interleukin: 1 or 3µg/kg ip Testing on days 2 and 15	Evidence that PB potentiated auditory startle responses in the presence of odors associated with stressors
Motor Function		
Abdullah et al., 2011 Mice	PB + permethrin Single dose of 2 mg/kg PB and/or 200 mg/kg permethrin in DMSO, or DMSO only, ip for 10 d. 115-d observation period.	Evidence of reduction in locomotor activity 30 days postexposure
Abou-Donia et al., 2001 Rats	DEET + PB + permethrin 1: 1.3mg/kg PB for days 30-45 2: 40 mg/kg/d DEET dermally 3: 0.13 mg/kg/d permethrin dermally 4: DEET + permethrin 5: DEET + PB 6: permethrin + PB 7: DEET + permethrin +PB 45 days	Evidence that PB increased beam walk latency, but not other measures of motor function
Abou-Donia et al., 2002 Rats	PB + sarin 1: 1.3 mg/kg/d PB for 15 days 2: 50, 75, 90, or 100 µg/kg sarin on day 15 3: PB + sarin	Evidence of impaired motor function
Abou-Donia et al., 2004 Rats	DEET + PB + permethrin 1: controls, 70% ethanol dermally and water by gavage 2: PB (0.13, 1.3, or 13 mg/kg/d) for days 46 to 60 3: PB + DEET (DEET at 4, 40, or 400 mg/kg/d for 60 days dermally) 4: PB + permethrin (permethrin at 0.013, 0.13 or 1.3 mg/kg/d for 60 days) 5: PB + DEET + permethrin	Evidence that PB, PB + DEET, and DEET + Per impaired motor function (beam walk time, incline plane performance, and grip strength)
Conn et al., 2002 Rats	Stress (heat) + sarin Stress 25°C or 32°C for 1h/day for 1, 5, or 10 days Sarin 0, 0.2, 0.4 mg/m^3 by inhalation Assessed for 1 month postexposure	No evidence of effect on activity levels
Dubovicky et al., 2007 Mice	PB + stress (chronic shaker) PB 10 mg/kg/day sc for 7 d Assessed on days 2 and 7 during stress and days 7, 14, 21 and 28 after treatment. Separate group of mice tested in open field on day 1, 3, and 6 during stress and PB	No evidence of effect of PB on locomotor activity
Hattiangady et al., 2014 Rats	DEET + PB + permethrin + stress Treatment group: 40 mg/kg/d DEET dermally + 0.13 mg/kg/d permethrin dermally + 1.3 mg/kg/d PB by gavage + 5 min/d restraint	Evidence of reduced locomotor activity in one test (voluntary wheel running) but no effect on other behaviors (open field test)

Study	Exposure	Result
	stress For 4 weeks; testing conducted 3 months postexposure	
Hoy et al., 2000a Rats	DEET + PB + permethrin 1: 10mg/kg PB by gavage 2: 50, 200, or 500 mg/kg DEET by gavage 3: 15, 30, or 60 mg/kg permethrin ip 4: 100 mg/kg DEET + 5 mg/kg PB 5: 15 mg/kg permethrin + 5 mg/kg PB; 6: 100 mg/kg DEET + 15 mg/kg permethrin Testing conducted 30 min after last treatment	Evidence of reduced locomotor speed in male rats exposed to PB + permethrin and DEET + permethrin
Hoy et al., 2000b Rats	DEET + PB + permethrin 1: 7.5 mg/kg PB by gavage 2: 200 mg/kg DEET by gavage 3: 60 mg/kg permethrin ip 4: 3.75 mg/kg PB + 30 mg/kg permethrin 5: 3.75 mg/kg PB + 100mg/kg DEET 6: 2.5 mg/kg PB + 20mg/kg permethrin + 67 mg/kg DEET 7: 100 mg/kg DEET + 30 mg/kg permethrin Daily for 7 days; testing conducted 24 hrs after last treatment	Evidence of reduced locomotor speed with PB + DEET
Mach et al., 2008 Mice	Stress + sarin Shaker stress 90 min/d for 7 days 6.4 μg/kg/d sarin on days 4-6 Tests conducted on days 5 and 7, and 21 days after exposure	Evidence of decreased locomotor activity
Reproductive System		
Abou-Donia et al., 2003 Rats	PB + permethrin + DEET + stress 1: 1.3 mg/kg/d PB in water 2: 0.13mg/kg/d permethrin dermally, and 40mg/kg/d DEET dermally 3: PB + permethrin + DEET + restraint stress 28 days	Evidence of sperm and testicular changes
Musculoskeletal System		
Husain and Somani, 2004 Mice	PB + sarin + stress 1: 0.01mg/kg/d sarin sc for weeks 5 and 6 2: exercise on treadmill daily for 10 weeks 3: sarin + exercise 4: 1.2 mg/kg/d PB orally for weeks 5 and 6 5: PB + exercise 6: PB + sarin 7: PB + sarin + exercise Animals sacrificed 24 hrs after last treatment	Evidence of effects on skeletal muscle (changes in muscle respiration)
Jagannathan et al., 2001 Mice	PB + stress 1: sedentary control 2: 1.2 mg/kg PB orally for weeks 5 and 6 3: PB + stress exercise daily for 10 weeks	Evidence of effects on skeletal muscle (changes in muscle respiration)

Study	Exposure	Result
	Sacrificed 24 hrs after last treatment	
Somani et al., 2000 Mice	PB + stress 1: sedentary control 2: stress exercise daily for 10 weeks 3: PB 1.2 mg/kg orally for weeks 5 and 6 4: PB + stress Sacrificed 24 hrs after last treatment	Evidence of effects on skeletal muscle (changes in muscle respiration)
Stevens et al., 2006 Marmosets	PB + vaccines; 1: 500 μg/kg/d PB days 15-44 2: vaccines at 20% of human dose days 0-51 3: vaccines + PB Animals sacrificed 18 months after first vaccinations	No evidence of effects on muscle function
Immune System		
Abdullah et al., 2011 Mice	PB + permethrin Single dose of 2 mg/kg PB and/or 200 mg/kg permethrin in DMSO, or DMSO only, ip for 10 d. 115-d observation period	Evidence of long-term immune effects
Griffiths et al., 2006 Marmosets	PB + vaccines 1: ten vaccines at 20% of human dose scheduled the same as service members, and 500 μg/kg/d PB between days 15 and 44 2: vaccines and saline	Little evidence of immune system impairment
Hornby et al., 2006 Marmosets	PB + vaccines 1: 500 μg/kg/d PB on days 15 and 44 2: vaccines at 20% of human dose between days 0–51 3: vaccines + PB	Little evidence of immune system impairment
Peden-Adam et al., 2001 Mice	DEET + PB + JP-8 Treatment: high or low dose,(single or combined mixture daily) 15.5 or 31 mg/kg DEET sc, 2 or 5 mg/kg PB orally, and 500 or 1000 mg/kg JP-8 by gavage 14 days	Little evidence of effects on immune function except for depression of plaque forming cells at both low and high dose combined treatments and a depression of delayed hypersensitivity response after the combined high dose treatment
Pain Response		
Nutter et al., 2013 Rats	PB + permethrin Treatment: 2.6 mg/kg/d permethrin dermally; 120 mg/kg chlorpyrifos sc every 14 days; 13 mg/kg/d PB by gavage on days 1–14 30 or 60 days; animals sacrificed 8 and 12 weeks postexposure	No evidence of effects on pain behavior or activity measures
Nutter and Cooper, 2014 Rats	PB + permethrin Treatment: 2.6 mg/kg/d permethrin dermally, 120 mg/kg chlorpyrifos sc every 14 days; 13mg/kg/d PB by gavage on days 1-14 30 or 60 days; animals sacrificed 8 and 12	Evidence of changes in pain behavior (prolonged rest period and decreased muscle press withdrawal) noted in treated animals during treatment but indices returned to normal after

Study	Exposure	Result
	weeks postexposure	cessation of treatment

NOTE: AChE = acetylcholinesterase; DEET = N,N-diethyl-meta-toluamide; DMSO = dimethyl sulfoxide; im = intramuscular; ip = intraperitoneal; JP-8 = jet propellant 8; PB = pyridostigmine bromide; sc = subcutaneous.

6

FINDINGS AND RECOMMENDATIONS

It has been more than 25 years since the 1990–1991 Gulf War ended. For over 15 years, committees of the Institute of Medicine (IOM, now part of the National Academies of Sciences, Engineering, and Medicine) have systematically examined the available clinical, epidemiologic, and toxicologic information in efforts to explain the multiple health problems of veterans who served in the 1990–1991 Gulf War. Those health conditions have included a constellation of symptoms, commonly grouped under the label of Gulf War illness. In the beginning of the *Gulf War and Health* series, in response to legislative mandates, the reports examined health effects that might have resulted from specific exposures to agents such as depleted uranium (DU), pyridostigmine bromide (PB), vaccines, nerve agents (e.g., sarin), insecticides, combustion products, solvents, and infectious agents. Later reports focused more on the specific health effects that might have resulted from deployment or combat, including traumatic brain injury, deployment-related stress, and blast injuries. Two prior reports and this volume focused generally on what health effects were seen more frequently or with greater severity in veterans who had deployed to the Persian Gulf region compared with veterans who had been in the military during the war but had not deployed to the Persian Gulf region or had deployed elsewhere. Conclusions from the IOM's series of *Gulf War and Health* reports have provided much useful information and have informed the Department of Veterans Affairs' (VA's) approach to providing both treatment and compensation to veterans.

Other organizations have also called for or undertaken research related to the health of Gulf War veterans. These organizations include the VA, the VA Research Advisory Committee on Gulf War Veterans' Illnesses (RAC), and the Department of Defense (DoD) through its Congressionally Directed Medical Research Program. Between 1994 and 2014, federal funding for research on Gulf War veterans health totaled more than $500 million (VA, 2015b).

In spite of the large amount of research, there remain substantive gaps in our understanding of the health effects resulting from deployment to the 1990–1991 Gulf War, and particularly with regard to the pathophysiology of Gulf War illness. Indeed, little progress has been made so far in identifying either specific causative agents or effective treatments, and Gulf War veterans and their families continue to report concerns about the war's health effects. In addition, the development of and treatment for the many persistent and debilitating symptoms that afflict some Gulf War veterans has continued to confound both the veterans and their health care providers.

In this chapter, the committee summarizes its findings and conclusions as reported in the previous chapters and provides recommendations on what it considered to be the most likely avenues of research that would facilitate a better understanding of the health problems associated with Gulf War deployments and their clinical management. It also provides recommendations

about areas where further research is unlikely to yield important and clinically applicable gains. Although the Volume 10 committee focused on the epidemiologic literature in making its findings, it also attempted to look at the literature broadly to identify information that might provide a more comprehensive understanding of the illnesses affecting Gulf War veterans. For example, the committee considered several new and rapidly emerging areas of scientific inquiry made possible by recent advances in genetics, immunology, and neuroimaging among other diagnostic advances.

SUMMARY OF FINDINGS

In spite of a thorough literature search, the Volume 10 committee found scant evidence to warrant changes to the conclusions made by the Volume 8 committee regarding the strength of the association between deployment to the Gulf War and adverse health conditions. Thus, veterans who were deployed to the Gulf War appear to have an increased risk for mental health disorders such as posttraumatic stress disorder (PTSD), generalized anxiety disorder, depression, and substance abuse, as well as Gulf War illness, chronic fatigue syndrome, and functional gastrointestinal conditions. Indeed, the constellation of symptoms and symptom clusters referred to as Gulf War illness (e.g., fatigue, muscle and joint pain, and cognitive problems) is the signature adverse health condition of having served in the Persian Gulf region. Multiple studies found that some Gulf War veterans, regardless of their country of origin and their different deployment-related exposures, have persistent, debilitating, and varying symptoms of Gulf War illness.

For several health conditions only one study, or in some cases no studies, were of sufficient quality to meet the criteria for a primary study (see Chapter 2 for a description of the criteria for primary and secondary studies). For health conditions for which new evidence was available, the data tended to support conclusions that generally were in accordance with the findings of prior Gulf War and Health committees. The conclusions of the Volume 10 committee are presented in Box 6-1.

Many of the *Gulf War and Health* reports emphasized the lack of information, and especially exposure information, on which to base definitive conclusions regarding the strength of the association between serving in the Gulf region and given health effects, particularly those conditions that have a long latency period. The lack of specific individual exposure information is not unexpected in wartime situations, but it nonetheless limits the ability to draw conclusions about observed health effects. Importantly, this committee finds no reason to believe that additional or better information about veteran exposures will ever become available, which at this point in time materially influences what further investigations are reasonable to pursue.

Although the committee considered the literature for all health conditions reported in Gulf War veterans without preconceived ideas about what those outcomes might be, the committee's statement of task required it to pay particular attention to several specific health outcomes: neurologic outcomes (e.g., Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis [ALS], and migraines), cancer (brain and lung cancer, in particular), and chronic multisymptom illness (called Gulf War illness in this report). Those health conditions were discussed in detail in Chapter 4 and are summarized briefly in the following sections. These are followed by additional recommendations related to considerations of exposures and health

effects; sex-, race- and ethnicity-specific effects; and future research directions for Gulf War illness.

BOX 6-1
Summary of Conclusions Regarding Associations Between Deployment to the Gulf War and Specific Health Conditions

Sufficient Evidence of a Causal Relationship

- Posttraumatic stress disorder (PTSD)

Sufficient Evidence of an Association

- Generalized anxiety disorder, depression, and substance abuse (particularly alcohol abuse)
- Gastrointestinal symptoms consistent with functional gastrointestinal disorders such as irritable bowel syndrome and functional dyspepsia
- Chronic fatigue syndrome
- Gulf War illness

Limited/Suggestive Evidence of an Association

- Amyotrophic lateral sclerosis (ALS)
- Fibromyalgia and chronic widespread pain
- Self-reported sexual difficulties

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

- Any cancer
- Cardiovascular conditions or conditions of the blood and blood-forming organs
- Endocrine and metabolic conditions
- Neurodegenerative diseases other than ALS
- Neurocognitive and neurobehavioral performance
- Migraines and other headache disorders
- Other neurologic outcomes
- Respiratory diseases
- Structural gastrointestinal diseases
- Chronic skin conditions
- Musculoskeletal system diseases
- Genitourinary conditions
- Specific birth defects
- Adverse pregnancy outcomes such as miscarriage, stillbirth, preterm birth, and low birth weight
- Fertility problems
- Increased mortality from any cancer, any neurologic disease (including multiple sclerosis, Alzheimer's disease, Parkinson's disease, and ALS), respiratory disease, or gastrointestinal disease

Limited/Suggestive Evidence of No Association

- Objective measures of peripheral neurologic conditions
- Multiple sclerosis
- Mortality from cardiovascular disease or parasitic diseases
- Decreased lung function
- Mortality due to mechanical trauma or other external causes

GULF WAR ILLNESS

The Volume 10 committee's statement of task asked it to comprehensively review, evaluate, and summarize the available scientific and medical literature regarding chronic multisymptom illness that is commonly known as Gulf War illness. In spite of over 2 decades of studies to help define, diagnose, determine its cause, and treat the multitude of symptoms that characterize Gulf War illness, little progress has been made in elucidating the pathophysiologic mechanisms that underlie the condition, the exposures that may have caused it, or treatments that are generally effective for veterans who suffer from it. The Volume 4 committee indicated that deployed veterans suffer from more signs and symptoms (e.g., headache, joint and back pain, fatigue and sleep problems, and cognitive dysfunction) than nondeployed veterans. The increased prevalence of diverse symptoms has been seen in Gulf War veterans from the United States as well as several of the coalition countries (e.g., Australia, United Kingdom, Canada), as well as in Danish veterans who served as peacekeepers after the conflict ended. The literature described in Volume 8 and in this volume provides further support for the conclusion that there is sufficient evidence of an association between deployment to the Gulf War and Gulf War illness. It must be noted, however, that some nondeployed veterans have symptoms that mirror Gulf War illness in spite of never having served in the Gulf region.

Over the last 25 years, many research efforts have been conducted in attempts to further understand Gulf War illness, including follow-up surveys of large samples of veterans to assess the prevalence and incidence of symptoms, clinical examinations of small groups of ill veterans, and animal toxicologic studies. Specialized studies have been conducted on various aspects of Gulf War illness including neurologic, autonomic, and immune function; genetic susceptibility; behavior; and quality of life. Chapter 3 described the many Gulf War veteran cohorts that have been studied and the numerous derivative studies on those cohorts that have looked at the prevalence and incidence of a variety of health conidtions. Other derivative studies have attempted to identify biological markers of disease and the interactions between health conditions in these veterans (e.g., Gulf War illness and obesity). Results from many of these studies have been summarized in Chapter 4. Because veterans' exposures were not uniform, some researchers have suggested that any associations have been obscured by investigations that look at veterans as a whole rather than by subgroups (White et al., 2015). While, in theory, analyses by subgroups of veterans defined by exposure, location, or other proxy might provide additional information, the available studies do not conduct such analyses nor is it likely that subgroups with known exposures can be reliably defined because there is no good exposure information on which to define them.

It is evident that Gulf War illness is the predominant health concern for many veterans, but as highlighted in this report and others (IOM, 2015), Gulf War illness is by no means an easily diagnosed condition. It presents with diverse symptom clusters, many of which overlap with other health conditions such as chronic fatigue syndrome, neurodegenerative disorders, and musculoskeletal problems, and there are multiple case definitions of it. In 2015, the IOM addressed the issue of a case definition of Gulf War illness and recommended that researchers use either the Centers for Disease Control and Prevention definition or the Kansas definition depending on the intent of the research (see the section on Gulf War illness in Chapter 4 for more information on the case definitions).

Although there has been a substantial body and a broad basis of research on Gulf War veterans, there are still substantial gaps and limitations in the body of evidence regarding the

health effects of deployment to the Gulf War, and Gulf War illness in particular. This committee echoes the concerns stated in earlier volumes: why do some veterans have a multitude of symptoms of Gulf War illness whereas others have only a few symptoms, and other veterans who served in the same area with seemingly similar exposures remain entirely without symptoms? Why do some veterans who were not on the ground in the Persian Gulf region such as the majority of the Australian forces, or who served after the war as peacekeepers, such as the Danish forces, or who were not near the Khamisiyah demolition area such as the British forces, also experience symptoms of Gulf War illness? Unfortunately, given the inconsistency and lack of replication of results and the often limited research methods, there is little reliable information on which to base a comprehensive view of Gulf War illness. Furthermore, varying definitions of Gulf War illness add to the confusion regarding its study and makes replicating results and meta-analyses across studies problematic.

A continuing problem with studying Gulf War illness is that most of the studies have excluded important psychophysiological aspects of the illness with regard to both diagnosis and treatment, in spite of veterans identifying symptoms such as chronic pain and sleep disturbances that may be amenable to psychophysiological therapies, alone or in conjunction with other treatments. Based on available research data, it does not appear that a single mechanism can explain the multitude of symptoms seen in Gulf War illness, and it is unlikely that a single definitive causal agent will be identified this many years after the war. The Gulf War and Health committee that assessed the effects of deployment-related stress on the physiological and psychological health of Gulf War veterans (IOM, 2008) found that such stress, which can arise from many different stimuli, such as hearing chemical alarms to seeing dead bodies or using pesticides to keep away sand fleas, can result in short-term and long-term physical reactions. That committee stated the following:

> The stress response is a coordinated set of interactions among multiple organ systems in the body, including the brain, gut, heart, liver, immune system, thyroid, adrenals, pituitary, gonads, bone, and skin. In response to a stressor, the body initiates an acute stress response… Activation of the stress response ensures survival in the short term, but is maladaptive when its activation persists as a result of chronic, severe, or repeated stress. Chronic stress can lead to adverse health outcomes that affect multiple body systems such as the [central nervous system] CNS and the endocrine, immune, gastrointestinal, and cardiovascular systems. Stress-induced abnormalities are due to dysregulation of a common set of mediators: cortisol, epinephrine, and immune system cytokines. The model of stress-related illness is built on evidence of interrelationships between stress hormones and other systems, including the endocrine and immune systems. Stress hormones can trigger interactions between the endocrine and immune systems that culminate in a state of chronic inflammation. Stress-induced chronic inflammation appears to be a driving force behind wide-ranging conditions linked to stress, such as obesity, heart disease, diabetes, and chronic pain (Black and Garbutt 2002; Black et al. 2006; Malarkey and Mills 2007).

The Volume 10 committee emphasizes that the deployment-related chronic health effects include many of those that characterize Gulf War illness.

Emerging diagnostic technologies and personalized approaches to medical care offer promise for the conduct of sufficiently powered research on the diagnosis and treatment of Gulf War illness. As stated by the Volume 8 committee (IOM, 2010) and concurred with by the Volume 10 committee

> (with) steady advances in understanding genetics, molecular diagnostics, and imaging, it is possible now to plan and carry out adequately powered studies to identify inherited genetic variants, molecular profiles of gene expression, other epigenetic markers (such as modifications of DNA structure related to environmental exposures), specific viral exposures, signatures of immune activation, or brain changes identified by sensitive imaging measures.

For example, it may be productive to conduct transcriptomic studies if the study protocols had methodological enhancements such as expanding the size of the study cohorts so the studies were robustly powered; using distinct discovery and replication cohorts, again each appropriately powered; using RNAseq methods which allow for analysis of sequences and numbers of all coding and noncoding RNA transcripts in an unbiased manner; using appropriately chosen control groups; and using appropriate bioinformatics tools to discern specific disease pathways.

Many efforts have been directed at linking Gulf War illness to one or more exposures that occurred in the Persian Gulf region using animal models and mixtures of chemical such as PB, DEET, and chlorpyrifos (see Chapter 5). Although animal studies have suggested some physiological and structural alterations in response to the chemical exposures that Gulf War veterans might have experienced while deployed, they have typically examined isolated symptoms of Gulf War illness rather than the constellation of symptoms reported by Gulf War veterans. Furthermore, the animal studies conducted to date have provided inconsistent results. Thus, in general, animal studies that attempt to mimic Gulf War illness have provided little in the way of helpful information because it is difficult to establish experimental exposures that replicate those experienced by Gulf War veterans during deployment when actual exposures are uncertain. Therefore, the committee concludes that although the existence of an animal model would be advantageous for identifying and evaluating treatment strategies for Gulf War illness, it cautions that developing such an animal model for Gulf War illness is not possible, given researchers' inability to realistically determine the exposures associated with Gulf War service, let alone the frequency, duration, or dose of those exposures, or the effect of multiple exposures.

In consideration of these things, the committee makes the following recommendations:

Recommendation: Any future studies of Gulf War illness should recognize the connections and complex relationships between brain and physical functioning and should not exclude any aspect of the illness with regard to improving its diagnosis and treatment.

Recommendation: The Department of Veterans Affairs and the Department of Defense should develop a joint and cohesive strategy on incorporating emerging diagnostic technologies and personalized approaches to medical care into sufficiently powered future research to inform studies of Gulf War illness and related health conditions.

NEUROLOGICAL CONDITIONS

The Volume 10 committee was specifically tasked with assessing the association between deployment to the Persian Gulf region and the prevalence of neurologic conditions, particularly Parkinson's disease, multiple sclerosis, ALS, and migraines. As described in Chapter 4, the committee considered each of these neurologic conditions separately.

The new evidence for multiple sclerosis, combined with that from Volume 8, suggests that in spite of studies which looked specifically for the disease in Gulf War veterans, there is limited/suggestive evidence of no association between deployment to the Gulf War and multiple sclerosis.

ALS is the only neurologic disease for which both this committee and the Volume 8 committee found limited/suggestive evidence of an association with deployment to the Gulf War. A previous IOM committee (IOM, 2006a) also noted that in the early years after the war, there was limited/suggestive evidence of an increase in the incidence of ALS in deployed veterans. Given that ALS and other neurodegenerative diseases are age-dependent, further surveillance in this population is warranted. Although Gulf War deployment was associated with increased risk of developing ALS and increased ALS severity, no association with ALS mortality (a uniformly fatal disease) was found. Thus, more research is warranted to clarify potential associations between ALS and Gulf War deployment.

The committee did not find that sufficient time has elapsed to assess whether any deployment-related exposures might have increased the occurrence of other neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and related disorders. Thus, the committee found that there continues to be inadequate or insufficient evidence to indicate any association between deployment to the Gulf War and neurodegenerative diseases other than ALS.

A conclusion of inadequate or insufficient evidence was also reached for the association of deployment to the Gulf War with migraines, which was considered specifically for the first time in this volume. The committee notes, however, that many of the health assessments on Gulf War veterans explored the presence of headaches but did not specifically ask about migraines. Therefore, the committee cautions that the occurrence of migraines in Gulf War veterans may be imprecisely established, in light of the uncertainty of subjective reports.

Given the substantial growth in the field of genetics and epigenetics as it relates to complex illness, some diseases studied relative to Gulf War deployment might be further informed by inclusion of genetic research aims. Specifically, in those diseases in which there is a highly penetrant, frequently present, and feasibly measured genetic risk marker, inclusion of these factors should be strongly considered when exploring the relationships between Gulf War deployment and subsequent disease. Among the relevant examples are the neurodegenerative diseases, which the committee anticipates will become more relevant for study over time, given their typically long latency and an aging veteran population. It will be of critical importance, however, that studies to identify novel genetic risk factors be robustly powered and appropriately designed to include both discovery and replication data. Until these approaches are considered, the committee anticipates substantial difficulty in better understanding the complexities associated with these neurodegenerative disorders in Gulf War veterans.

Recommendation: The Department of Veterans Affairs should continue to conduct follow-up assessments of Gulf War veterans for neurodegenerative diseases that

have long latencies and are associated with aging; these include amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease.

LUNG AND BRAIN CANCER

The Volumes 8 and 10 committees were asked to specifically consider whether Gulf War veterans were at increased risk for developing any form of brain cancer, a relatively rare cancer. The Volume 4 committee described one mortality study of Gulf War veterans that found an increased risk of dying from brain cancer in deployed veterans through 2000. The increased risk was associated with being exposed to the nerve agents at Khamisiyah with a dose–response that corresponded to the duration of exposure (0 vs 1 vs ≥ 2 days). That committee noted that brain cancer typically has a latency period of 10–20 years and thus the increase seen at about 9 years after exposure needed to be interpreted with caution. The Volume 8 committee found one additional study of brain cancer that was a 4-year follow-up to the earlier mortality study (Barth et al., 2009). Barth et al. (2009) failed to show an increased risk of dying from brain cancer in the deployed versus nondeployed veterans, but did report that 2 or more days of exposure to nerve agents at Khamisiyah and exposure to smoke from oil-well fires were both significantly associated with an increased risk of brain cancer mortality. Exposures to the nerve agents and to the smoke from oil-well fires, however, were both determined by modeling, and GAO (2004) reported that the modeling had serious limitations. These model limitations make it impossible to determine individual service member exposures and therefore to link the modeled exposures to health outcomes. The four new studies identified by the Volume 10 committee found no statistically significant increased risk of brain cancer in Australian or U.S. Gulf War veterans compared with their nondeployed counterparts, although the power of the Australian study to detect rare cancers such as brain cancer was low. Overall, the studies indicate that the evidence for an association between deployment to the Gulf War and brain cancer is inadequate/insufficient.

The Volumes 4 and 8 committees found no evidence to indicate that Gulf War veterans were at increased risk for lung cancer in the approximately 10–15 years after the war, but the Volume 10 committee emphasizes that lung cancer may have a latency of longer than 15 years and that studies to date are not sufficient to exclude a higher risk of lung cancer among Gulf War veterans. This committee reviewed one large study of U.S. Gulf War veterans that found an increased incidence of lung cancer based on state and VA cancer registry data from 1991 to 2006 for deployed versus nondeployed veterans, but neither veteran group had a greater risk when compared with the general population. Importantly, as the committee noted in Chapter 4, this new study provided no information on smoking behavior among the veterans. Since about 90% of lung cancer in the United States is related to smoking, the lack of smoking information materially precludes interpretation of the study's finding. In spite of this limitation, the committee found the pooling of data across registries to be a good approach for increasing the sample size and thus the power of the study.

In summary, the Volume 10 committee finds that the evidence continues to be inadequate/insufficient to determine whether deployed Gulf War veterans are at increased risk of developing any cancer, including lung cancer and brain cancer. The relative rarity of cancers such as brain cancer argues for larger studies with adequate statistical power. This may require pooling data where feasible and the use of a variety of data sources such as state cancer registries.

Recommendation: The Department of Veterans Affairs should conduct further assessments of cancer incidence, prevalence, and mortality because of the long latency of some cancers. Such studies should maximize the use of cancer registries and other relevant sources, data, and approaches, and should have sufficient sample sizes to account for relatively rare cancers. These studies should also be able to report sex-specific and race/ethnicity-specific information.

OTHER HEALTH CONDITIONS

In contrast to cancer, the committee finds that sufficient time has elapsed to determine that Gulf War veterans do not have an increased incidence of circulatory, hematologic, musculoskeletal, gastrointestinal, genitourinary, reproductive, and chronic skin conditions. The committee is also cognizant of the fact that as Gulf War veterans age, it will be more difficult to differentiate the effects of deployment from the natural effects of aging on morbidity and mortality.

The committee finds that the association of service in the Gulf War with PTSD, anxiety disorders, substance abuse, and depression is now well established and further studies to assess whether there is an association are not warranted.

There are no data suggesting delayed effects of Gulf War exposures that might have arisen from such chemicals as nerve agents or PB. Furthermore, the serum half-lives of chemicals such as nerve agents and PB are not consistent with their long-term retention in the body; such retention would be necessary to cause adverse health effects years after exposure (IOM, 2000, 2004). Thus, the committee finds that it is not reasonable to expect new onset of disease, with the exception of diseases with especially long latency periods such as some types of cancer.

Recommendation: Further studies to assess the incidence and prevalence of circulatory, hematologic, musculoskeletal, gastrointestinal, genitourinary, reproductive, endocrine and metabolic, respiratory, chronic skin, and mental health conditions due to deployment in the Gulf War should not be undertaken. Rather, future research related to these conditions should focus on ensuring that Gulf War veterans with them receive timely and effective treatment.

EXPOSURE ASSESSMENTS

Chief among the concerns of the Gulf War and Health committees, including this committee, has been the lack of reliable exposure information about the environmental and occupational agents in the Persian Gulf region. Beginning with Volume 1, IOM committees have noted that environmental sampling was not conducted during the war, making it virtually impossible to know the particular agents that were present, let alone the potential frequency, intensity, or duration of individual exposures to such agents. Furthermore, as noted in Chapter 2, exposures were neither isolated nor due to single agents; veterans were typically exposed to multiple agents in varying combinations of varying duration and intensity during deployments. Record keeping for exposures such as vaccines was poor, some veterans self-administered agents (e.g., insecticides for sand fleas and PB when chemical alarms sounded), and some exposures

were ubiquitous (e.g., smoke from oil-well fires, high ambient temperatures, and sand). Many veterans continue to be concerned about the health effects stemming from possible exposure to sarin and cyclosarin after the demolition of munitions at Khamisiyah. Modeling efforts to identify veterans who may have been exposed to the nerve agents have proven to be problematic and not reassuring to the thousands of veterans who continue to experience unexplained symptoms. Both false positive (self-reporting exposure but no exposure occurred) and false negative (self-reporting no exposure when an exposure actually occurred but the veteran was not aware of it) reporting baises are possible with respect to exposure.

Even today, some researchers continue to try to assess veterans' exposures using surveys. As stated by the Volume 8 committee and strongly endorsed by this committee, "At almost 2[5] years after the war, it is difficult, if not impossible, to reconstruct the exposures to which the veterans were subjected in theater." Given the lack of objective exposure information at an individual level (except for DU), the committee concludes that further studies aimed at determining cause-and-effect relationships between Gulf War exposures and health effects seen in Gulf War veterans are unlikely to produce useful information. Although military records for veterans of coalition countries may have more information on administration of vaccines and other medical procedures, the applicability of such data to U.S. Gulf War forces is uncertain.

Although many animal studies have attempted to simulate exposure scenarios that mimic possible chemical exposures that occurred during the Gulf War, this has proven to be difficult and the test mixtures and doses are not necessarily representative of the real-world exposures experienced by veterans during deployment. For example, as discussed in Chapter 5, some researchers have developed exposure scenarios for animal models of Gulf War illness that have generally included some combination of sarin, DEET, permethrin, paraoxon, and chlorpyrifos, with a physical stressor such as heat or forced swimming. How accurately these exposures simulate the exposures in the Persian Gulf region is not possible to determine. Furthermore, common stressors experienced by the veterans such as exposure to combustion products, diesel fumes, solvents, and other pesticides are not included in these animal models. Overall, while these studies may be interesting, or even intriguing, and may eventually be helpful in identifying markers of illness or treatment, the applicability of those exposures to what actually occurred in the Gulf War illness is uncertain.

One exception to the inability to reliably determine Gulf War exposures is DU. The surveillance program at the University of Maryland that is monitoring the long-term health effects of embedded DU in a group of Gulf War veterans (i.e., studies by McDiarmid and colleagues) is the only instance of a successful exposure assessment in veterans because DU can be measured in human tissue over time.

For future conflicts, collecting exposure information before, during the deployments, and afterwards, preferably using environmental and individual monitoring devices and military records (both health and administrative) to capture such information as vaccines, troop location, and toxicant concentrations, would make the data less subject to recall bias and permit a more accurate assessment of actual exposures.

Recommendation: Without definitive and verifiable individual veteran exposure information, further studies to determine cause-and-effect relationships between Gulf War exposures and health conditions seen in Gulf War veterans should not be undertaken.

SEX, RACE, AND ETHNICITY

An unprecedented number of women deployed to the Gulf War (almost 50,000), and this was the first war in which women were deployed to combat zones, but few data are available on the health of those women. And while the proportion of women who served in the Gulf War was less than the number of women who have served in the conflicts in Iraq and Afghanistan, it is nonetheless important to assess and report on their health status so that health patterns over time and historical exposures can be understood and be used to improve women veterans' health and potentially avoid problems in the future.

As female Gulf War veterans age, it is important to track morbidity and mortality trends among this not insignificant number of women. The Volume 8 committee noted that "Female Gulf War veterans experienced many of the exposures and stressors that male Gulf War veterans experienced while deployed to the Persian Gulf region in 1990–1991." And although women were excluded from combat roles per se, they were deployed to combat zones. They were more likely to have experienced sexual harassment or assault while deployed than men.

Women may have different responses to stress and other exposures than men and, thus, may have different health consequences. For example, three out of four people who have migraines are women, and women tend to have more severe migraines (womenshealth.gov, accessed November 12, 2015). Women also have different risk profiles for cardiovascular disease, musculoskeletal disorders, and some cancers.

In a similar manner, health risks for race and ethnic minority veterans may also be different. Genetic risks for some diseases vary across race and ethnicities, for example, blacks are at greater risk for some genetic causes of ALS and for heart disease than whites. Even among Gulf War veterans, racial differences are seen. For example, Hispanic and black Gulf War veterans reported increased rates of PTSD, major depressive disorder, and Gulf War illness (Coughlin et al., 2011b), as well as neurological conditions and multiple sclerosis (Wallin et al. 2012), compared with white Gulf War veterans.

Notwithstanding well-established differences in health conditions according to sex and race/ethnicity, few studies on Gulf War veterans specifically report outcomes for women or racial/ethnic minorities, although many veteran studies adjust for sex and race/ethnicity in their analyses. This lack of distinction is important and makes it imperative that researchers report sex- and race/ethnicity-specific outcomes, particularly in large cohorts. For example, in large studies such as the VA National Health Survey of Gulf War Veterans and Their Families, data on the health of women and race/ethnicity groups are collected, but are rarely reported as sex- or race/ethnicity-specific outcomes. Research on women's health, including reproductive health, should seek to address stressors and exposures that women in the military may experience. For example, new research suggests that stress exposure in young women may cause gynecologic effects that may be associated with early menopause (Bleil et al., 2012). Assessing the incidence of early menopause among female Gulf War veterans would be helpful in determining the link between deployment stress and health conditions in women and the possible need for early screening of these women for estrogen-related cancers. Overall, the committee concludes that, to date, studies of Gulf War veterans have not adequately considered sex- and race/ethnicity-specific health conditions.

Recommendation: Sex-specific and race/ethnicity-specific health conditions should be determined and reported in future studies of Gulf War veterans. In addition,

selected prior studies (e.g., large cohort studies) should be reviewed to determine whether reanalysis of the data to assess for possible sex-specific and race/ethnicity-specific health conditions is feasible.

MOVING FORWARD

Beginning with Volume 1 of the *Gulf War and Health* series, numerous IOM committees have reviewed the literature on the health of Gulf War veterans. Although there have been some variations, generally, the results have been remarkably consistent. What is striking about this and prior Gulf War and Health committees' findings is that the health conditions found to be associated with Gulf War deployment are primarily mental health disorders and functional medical disorders. What links these conditions is that they have no objective medical diagnostic tests and are diagnosed based on subjective symptom reporting. These associations emphasize the interconnectedness of the brain and body.

The committee concludes that it is time research efforts move forward and focus on this interconnectedness when seeking to improve treatment of veterans for Gulf War illness. Further exploration of symptom management approaches and treatments for Gulf War illness, even in the absence of definitive etiologies, is warranted, as is the case with so many other medical conditions. Researchers have already conducted some clinical trials based on therapies that have previously shown benefits for conditions characterized by symptoms having unexplained etiologies. Therefore, Gulf War illness research should be realigned to focus on the treatment of its complex symptomatology rather than causal mechanisms. Such research should recognize the growing evidentiary base demonstrating an intricate brain–body relationship and complex relationships between brain and physical functions. For example, as noted earlier, the acute response to an exposure that causes stress (physiologic or psychologic) involves interactions among multiple organs and organ systems, including the brain, gastrointestinal tract, heart and circulatory system, liver, immune system, thyroid, adrenals and pituitary glands, gonads, bone, and skin. Acute and chronic health effects of stress on workers in diverse occupations (e.g., firefighters, bus drivers, computer operators, emergency services personnel, police officers, and nurses) have been well documented in recent years. Clearly, a stress response, such as could occur in a war zone, results in a cascade of physiologic changes that can have profound and lasting effects on multiple organ systems. To ignore available treatments that may improve the functioning of any of these organ systems is to do a disservice to our Gulf War veterans.

Recommendation: Future Gulf War research should place top priority on the identification and development of effective therapeutic interventions and management strategies for Gulf War illness. The Department of Veterans Affairs should support research to determine how such treatments can be widely disseminated and implemented in all health care settings.

7

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APPENDIX

COMMITTEE BIOGRAPHIES

Deborah A. Cory-Slechta, Ph.D. (Chair), is a professor of Environmental Medicine and Pediatrics at the University of Rochester School of Medicine and Dentistry. She was formerly Dean for Research and Chair of the Department of Environmental Medicine at the University of Rochester School of Medicine and Dentistry. She has also served as director of the Environmental and Occupational Health Sciences Institute and Chair of the Department of Environmental and Occupational Medicine at the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School. Her research interests include the relationships between neurotransmitter systems and behavior, and how such relationships are altered by exposure to environmental toxicants, particularly the role of environmental neurotoxicants in developmental disabilities and neurodegenerative diseases. Dr. Cory-Slechta has served on numerous national research review and advisory panels, including those for the National Institutes of Health (NIH), the U.S. Environmental Protection Agency (EPA), and the Centers for Disease Control and Prevention (CDC). She served on the National Research Council's (NRC) Committee on Human Health Risks of Trichloroethylene and the Committee on Toxicology and on the Institute of Medicine's (IOM) Committee on Gulf War and Health: Literature Review of Pesticides and Solvents. She received her Ph.D. from the University of Minnesota.

Robert H. Brown, Jr., M.D., D.Phil., is professor and Chair of Neurology at the University of Massachusetts Medical Center and Medical School. He is also the Director of the Day Neuromuscular Research Laboratory at the University of Massachusetts Medical School. Dr. Brown's laboratory has focused on the identification of gene defects that elucidate the molecular pathogenesis of selected neuromuscular diseases including amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), muscular dystrophy, adrenoleukodystrophy, hereditary neuropathy and hyperkalemic periodic paralysis. Knowledge of theses disease genes has facilitated the creation of mouse and cell-based models of these disorders. In turn, these resources have allowed study of therapeutic strategies using conventional small molecule approaches and new modalities such as inhibitory RNAi. Dr. Brown is a member of the National Academy of Medicine. He previously served on the IOM Committee on Gulf War and Health: Health Effects of Serving in the Gulf War, Update 2009. Dr. Brown earned a medical degree from Harvard Medical School and a doctoratal degree in neurophysiology from Oxford University.

Alberto Caban-Martinez, D.O., Ph.D., M.P.H., is an assistant professor of Public Health Sciences in the Division of Environment and Public Health of the Department of Public Health Sciences at the University of Miami Miller School of Medicine; Instructor of Orthopedic Surgery at Harvard Medical School and Research Associate at the Harvard School of Public Health. He is the Director of the Musculoskeletal Disorders and Occupational Health Lab and Associate Director of the Miami Occupational Research Group. His primary area of research concerns the prevention of musculoskeletal disorders among U.S. workers including two studies: the National

Institute of Occupational Safety and Health (NIOSH)-funded Musculoskeletal Study of Construction workers' Longitudinal Exposures, a cohort of 500 commercial construction workers; and the Home Health Occupations–Musculoskeletal Examinations, a mixed-methods pilot research study in minority home health workers. He is a standing member of the NIOSH National Occupational Research Agenda Construction Sector and Mining Sector Council. He conducted postdoctoral research in the Department of Environmental Health at the Harvard School of Public Health. Dr. Caban-Martinez is currently board certified in public health. He received his Ph.D. from the Department of Epidemiology and Public Health at the University of Miami, Miller School of Medicine and attended medical school at Nova Southeastern University College of Osteopathic Medicine.

Javier I. Escobar, M.D., M.Sc., is associate dean for global health and professor of psychiatry and family medicine at the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School. He has been an active researcher in clinical psychopharmacology, psychiatry, psychiatric epidemiology, psychiatric diagnosis, cross-cultural medicine, mental disorders in primary care, and treatment of somatoform disorders. Dr. Escobar has been the principal investigator of several NIH–funded grants in medically unexplained symptoms, mentoring of young researchers, and mental-health–primary-care collaborations. He has published more than 200 scientific articles in books and journals and has served on a number of advisory committees and task forces, including those for the National Institute of Mental Health, the World Health Organization, the Food and Drug Administration, the Department of Veterans Affairs, and the Robert Wood Johnson Foundation. Dr. Escobar recently served on the IOM Committee on Gulf War and Health: Treatment of Chronic Multisymptom Illness. He received his M.D. from Universidad de Antioquia, Medellin, Colombia and did his specialty training and obtained a master's degree in psychiatry–medical genetics at the University of Minnesota.

Scott Fishman, M.D., is professor of anesthesiology and Chief of Pain Medicine at the University of California, Davis, Health System. His research is focused on chronic pain, cancer pain management, psychiatric issues of chronic illness and pain, neuropathic pain treatment strategies, and medical informatics. Dr. Fishman has served on the board of directors of the American Pain Society and is Past President of the American Academy of Pain Medicine and is a member of the Pain Care Coalition. He is the senior editor of Pain Medicine. He is board certified in psychiatry, pain medicine and previously certified in Internal Medicine. He completed his medical degree at the University of Massachusetts Medical School.

Mary A. Fox, Ph.D., is assistant professor in the Department of Health Policy and Management and Co-Director of the Risk Sciences and Public Policy Institute at the Johns Hopkins Bloomberg School of Public Health. She teaches courses in quantitative risk assessment methods and risk policy and management for the Risk Sciences and Public Policy Institute's Certificate Program. Dr. Fox's research is focused on human health risk assessment as a part of environmental policy making, particularly approaches to cumulative and chemical mixtures risk assessment. Dr. Fox served on the IOM Committee on Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan, and served on the NRC Committee on the Health Risks of Phthalates. Dr. Fox began her public health career conducting community health studies around hazardous waste sites as a Research Scientist in the New York State Department of

Health. Dr. Fox received her M.P.H. from the University of Rochester School of Medicine and Dentistry and Ph.D. from the Johns Hopkins Bloomberg School of Public Health.

Herman Gibb, Ph.D., is president of Gibb Epidemiology Consulting, LLC, in Arlington, Virginia. Prior to forming Gibb Epidemiology Consulting, he was President of Tetra Tech Sciences where he consulted to a variety of government, private, and international clients. Before joining Tetra Tech in 2004, Dr. Gibb had a career at the U.S. Environmental Protection Agency where he participated in the epidemiologic assessment of a variety of substances and was the primary author of an influential study on the risk of lung cancer among chromium production workers. He was a member of the Carcinogen Assessment Group—the beginning of EPA's approach to carcinogen risk assessment, and is the recipient of numerous EPA awards including the Gold Medal for his work on the risk assessment of arsenic. He was an invited participant on all of the World Health Organization's (WHO) Final Review Boards on Concise International Chemical Assessment Documents and a member of WHO's Risk Assessment Steering Group. He is an author of WHO's Principles for the Assessment of Risks to Human Health from Exposure to Chemicals. In 2011, Dr. Gibb was awarded the Practitioner of the Year award by the Society for Risk Analysis. He currently chairs a WHO task force on chemicals in food. Dr. Gibb is a Lieutenant Colonel (ret.) U.S. Army Reserves. Dr. Gibb has a Ph.D. in epidemiology from Johns Hopkins University and an M.P.H. in environmental health from the University of Pittsburgh.

Rogene F. Henderson, Ph.D., is an emeritus senior biochemist and toxicologist in the Experimental Toxicology Program of the Lovelace Respiratory Research Institute. She is also a clinical professor in the College of Pharmacy at the University of New Mexico in Albuquerque. Her major research interests are in the use of bronchoalveolar lavage fluid analyses to detect and characterize biomarkers of developing lung disease, the toxicokinetics of inhaled vapors and gases, and the use of biological markers of exposure and of effects to link environmental exposure to disease. She has served on a number of scientific advisory boards, including those of the Department of Energy, EPA, National Institute of Environmental Health Sciences, WHO, and the U.S. Army. She was recently chair of EPA's Clean Air Scientific Advisory Committee. Dr. Henderson is a National Associate of the National Academies. She has served on 28 NRC committees, chairing eight of them. Dr. Henderson is currently chair of the National Academies of Sciences, Engineering and Medicine's Board on Environmental Studies and Toxicology, and she served for 8 years on the Research Committee of the Health Effects Institute (HEI). She received her Ph.D. in chemistry from the University of Texas.

Clifford Jack, M.D., is professor of radiology at the Mayo Clinic in Rochester, MN. His lab is engaged in brain imaging research in cognitive aging, Alzheimer's disease, and related disorders. Dr. Jack's research team employs a variety of MRI-based brain imaging modalities and positron emission tomography (PET) to study the biology of brain aging and causes of cognitive impairment and develops image-processing algorithms for quantitatively measuring the information obtained from brain imaging. The lab's clinical imaging research is tightly integrated into the Mayo Clinic Alzheimer's Disease Patient Registry (Mayo Clinic Study of Aging) and Mayo's Alzheimer's Disease Research Center, which conduct NIH-funded longitudinal clinical and epidemiological research projects investigating normal aging, Alzheimer's disease and other

dementias. Dr. Jack was elected to the National Academy of Medicine in 2013. He earned his medical degree from Wayne State University School of Medicine.

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Joel Kramer, Psy.D., is professor of Neuropsychology in Neurology and the Director of the Memory and Aging Center Neuropsychology program at the University of California, San Francisco. Dr. Kramer has been extensively involved in studying the cognitive changes associated with brain disorders for the past three decades. He has co-authored widely used neuropsychological measures of memory and executive functioning. Much of his work has been devoted to identifying the different ways in which aging and neurodegenerative diseases affect memory and other abilities and in utilizing these differences to improve differential diagnosis in clinic. Presently, Dr. Kramer's active areas of research use neuroimaging, neuropsychology, neuroimmunology, and genetics to study the underlying biological mechanisms of cognitive aging, the cognitive effects of cerebrovascular disease and frontotemporal dementia, and the relationships between cognitive functioning, behavioral control, and reward systems. Dr. Kramer

is board certified in clinical neuropsychology. He earned his doctorate in psychology at Baylor University and completed a postdoctoral fellowship in neuropsychology at the Martinez VA hospital.

Francine Laden, Sc.D., is the Professor of Environmental Epidemiology at the Harvard T.H. Chan School of Public Health. Additionally, she is an associate professor in the Department of Medicine, Harvard Medical School and assistant professor in the Department of Medicine, Brigham and Women's Hospital. Dr. Laden's research focuses on environmental risk factors of chronic disease, including cardiovascular disease and cancer, specifically breast cancer, non-Hodgkin's lymphoma (NHL), and lung cancer. Her current research focus is on the adverse effects of chronic exposures to air pollution and on the effects of the built environment and greenspace on health. She has served on two IOM committees on Gulf War and Health, the Committee on Gulf War and Health Volume 4: Review of the Medical Literature Relative to Gulf War Veteran's Health and Gulf War and Health Volume 8: The Committee on Gulf War and Health: Health Effects of Serving in the Gulf War, Update 2009; also served on the IOM committee on the Review of the Department of Labor's Site Exposure Matrix (SEM) Database, and the NRC Committee on Contaminated Drinking Water at Camp Lejeune. Dr. Laden received her Sc.D. from the Harvard School of Public Health.

James M. Noble, M.D., is assistant professor of Neurology at Columbia University Medical Center with the Taub Institute for Alzheimer's Disease and the Aging Brain at Columbia University. He received his medical degree from Emory University, trained in neurology residency and dementia fellowship at Columbia University Medical Center, and received a master's of science in epidemiology at the Mailman School of Public Health of Columbia University through the NIH supported neuroepidemiology training program at Columbia University. His clinical practice focuses on neurodegenerative forms of dementia including Alzheimer disease and related disorders. He leads several research projects including collegiate sports-related concussion and chronic traumatic encephalopathy, neurological health literacy, and systemic inflammatory markers as potential novel Alzheimer risk factors. He is board certified in neurology, behavioral neurology and neuropsychiatry, and public health.

Anbesaw Selassie, Dr.P.H., is associate professor of public health sciences at the Medical University of South Carolina. He is interested in the neuroepidemiology of central nervous system injuries and epilepsy, infectious disease epidemiology, and methodological issues in disease surveillance and outcome research. He completed masters and doctoral degrees in epidemiology and biostatistics at the University of South Carolina.

Nancy F. Woods, Ph.D., is professor of Biobehavioral Nursing and Health Systems at the University of Washington. She previously served as the dean of the University of Washington's School of Nursing and as the president of the American Academy of Nursing. She co-led a 20-year longitudinal study of women's experiences during the menopause transition and studied personal, social, endocrine, and aging-related factors influencing women's symptoms. She is currently involved in a collaborative study on the use and acceptability of electronic apps to help women identify their symptoms and communicate more clearly with their health care providers. She is an investigator for the Women's Health Initiative Study and has published results related to frailty in older women as well as healthy aging phenotypes, aging well, and well-being. She

leads the special interest group on Biology of Aging and Geriatrics for the National Academies of Sciences, Engineering, and Medicine, serves as a member of the American Academy of Nursing Expert Panel on Women's Health, and is President of the Washington State Academy of Science. Previously, Dr. Woods was a member of the 1996 IOM Committee to Review the Health Consequences of Service During the Persian Gulf War. Dr. Woods earned an M.N. from the University of Washington, a Ph.D. in Epidemiology from the University of North Carolina, Chapel Hill.