

Gulf War and Health

VOLUME 4

HEALTH EFFECTS OF SERVING IN THE GULF WAR

**Committee on Gulf War and Health: A Review of the Medical Literature Relative
to the Gulf War Veterans' Health**

Board on Population Health and Public Health Practice

**INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES**

SUMMARY

Although the 1990-1991 Persian Gulf War was considered a brief and successful military operation with few injuries and deaths among coalition forces, many returning veterans soon began reporting numerous health problems that they believed to be associated with their service in the Persian Gulf.

In 1998, in response to the growing concerns of the ill Gulf War veterans, Congress passed two laws: PL 105-277, the Persian Gulf War Veterans Act, and PL 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, and preventive medicines or vaccines associated with Gulf War service and to consider the NAS conclusions when making decisions about compensation. Those studies were assigned to the Institute of Medicine (IOM).

This study, conducted at the request of the Department of Veterans Affairs (VA), differs from the previous work of IOM in that it summarizes in one place the current status of health effects in veterans deployed to the Persian Gulf irrespective of exposure information. One can confidently assess health responses associated only with deployment in the Gulf War Theater. Estimating the veterans' health risks associated with particular environmental exposures is challenged by the lack of exposure monitoring and of biomarkers to quantify individual exposures of veterans during the deployment retrospectively.

CHARGE TO THE COMMITTEE

The charge to this IOM committee was to review, evaluate, and summarize peer-reviewed scientific and medical literature addressing the health status of Gulf War veterans. The study was to help to inform the VA of illnesses among Gulf War veterans that might not be immediately evident.

COMMITTEE'S APPROACH TO ITS CHARGE

The committee began its evaluation by presuming neither the existence nor the absence of illnesses associated with deployment. It sought to characterize and weigh the strengths and limitations of the available evidence. The committee did not concern itself with policy issues, such as decisions regarding disability, potential costs of compensation, or any broad policy implications of its findings.

Extensive searches of the scientific and medical literature were conducted, and over 4,000 potentially relevant references were retrieved. After assessment of the titles and abstracts references found in of the initial searches, the committee focused on 850 potentially relevant epidemiologic studies for its review and evaluation.

The committee limited its review of the literature primarily to epidemiologic studies of Gulf War veterans to determine the prevalence of diseases and symptoms in that population. Those studies typically examine veterans' health outcomes in comparison with outcomes in their nondeployed counterparts.

The committee decided to use only peer-reviewed published literature on which to base its conclusions. The process of peer review by fellow professionals increases the likelihood of a high-quality study but does not guarantee its validity or the generalizability of its findings to the entire group of subjects under review. 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 (exception to calculate response rates for consistency among studies).

After securing the full text of the peer-reviewed epidemiologic studies it would review, the committee determined which studies would be considered primary or secondary studies. Primary studies provide the basis of the committee's findings. To be included in the committee's review as a primary study, a study had to meet specified criteria. The criteria include studies that provide information about specific health outcomes, demonstrate rigorous methods, describe its methods in sufficient detail, include a control or reference group, have the statistical power to detect effects, and include reasonable adjustments for confounders. Other studies were considered secondary for the purpose of this review and provided background information or "context" for the report. Another step that the committee took in organizing its literature was to determine how all the studies were related to one another. Numerous Gulf War cohorts have been assembled, from several different countries; from those original cohorts many derivative studies have been conducted. The committee organized the literature into the major cohorts and derivative studies because they didn't want to interpret the findings of the same cohorts as though they were results from unique groups (Chapter 4).

LIMITATIONS OF THE GULF WAR STUDIES

Overall, the studies of Gulf War veterans' health are of varied quality. Although, they have provided valuable information, many of them have limitations that hinder accurate assessment of the veterans' health status. Common study limitations include use of a population that was not representative of the entire Gulf War population, reliance on self-reports rather than objective measures of symptoms, low participation rates, and a period of investigation that was too brief to detect health outcomes with long latency such as, cancer. In addition, many of the US studies are cross-sectional, and this limits the opportunity to learn about symptom duration, long-term health effects, latency of onset, and prognosis.

OVERVIEW OF HEALTH OUTCOMES

While examining health outcomes in Gulf War-deployed veterans, numerous researchers have attempted to determine whether a set of symptoms reported by veterans could be defined as a unique syndrome or illness. Investigators have attempted, by using factor or cluster analysis, to define a unique health outcome, but none has been identified. Every study reviewed by this committee found that veterans of the Gulf War report higher rates of nearly all symptoms examined than their nondeployed counterparts. That finding was applied not only to Gulf War veterans from the United States but also to the Gulf War veterans deployed from the UK, Canada, Australia, and Denmark. Some studies examined performance on neurocognitive tests in association with symptoms that were considered possibly indicative of neurological or cognitive impairment (such as headache, confusion, and memory problems). Those few studies seemed to indicate that Gulf War veterans with such symptoms demonstrated neurobehavioral deficits, but, most of the studies did not include control groups (or, in some cases, valid control groups).

In many studies, investigators found a higher prevalence not only of individual symptoms but also of chronic multisymptom illnesses among Gulf War-deployed veterans than among the nondeployed. Multisymptom-based medical conditions reported to occur more frequently among deployed Gulf War veterans include fibromyalgia, chronic fatigue syndrome (CFS), and multiple chemical sensitivity (MCS). However, the case definitions for those conditions are based on symptom reports, and there are no objective diagnostic criteria that can be used to validate the findings, so, it is not clear whether the literature supports a true excess of the conditions or whether the associations are spurious and result from the increased reporting of symptoms across the board. The literature also demonstrates that deployment places veterans at increased risk for symptoms that meet diagnostic criteria for a number of psychiatric illnesses, particularly posttraumatic stress disorder (PTSD), anxiety, depression, and substance abuse. In addition, comorbidities have been reported, for example, symptoms of both PTSD and depression. The committee felt confident that several studies validated the increased risk of psychiatric disorders.

Some studies indicate that Gulf War veterans are at increased risk for amyotrophic lateral sclerosis (ALS). With regard to birth defects, there is weaker evidence that Gulf War veterans' offspring might be at risk for some birth defects; the findings are inconsistent. There were increased rates of transportation-related injuries and mortality among deployed Gulf War veterans, however, that increase appears to have been restricted to the first several years after the war. Finally, long-term exacerbation of asthma appeared to be associated with oil-well fire smoke, but there were no objective measures of pulmonary function in the studies.

The health outcomes presented above are discussed in some detail in the following pages. They are grouped according to whether the findings were based on objective measures and diagnostic medical tests.

Outcomes Based Primarily on Symptoms or Self-Reports

The largest and most nationally representative survey of US veterans found that nearly 29% of deployed veterans met a case definition of "multisymptom illness", compared with 16% of nondeployed veterans. Those figures indicate that unexplained illnesses are the most prevalent health outcome of service in the Gulf War. Several researchers have tried to determine whether the symptoms that have been reported by Gulf War veterans cluster in such a way as to make up

a unique syndrome, such as “Gulf War illness”. The results of that research indicate that although deployed veterans report more symptoms and more severe symptoms than their nondeployed counterparts, there is not a unique symptom complex (or syndrome) in deployed Gulf War veterans.

Among the many symptoms reported by Gulf War veterans are deficits in neurocognitive ability. Obviously such reports are of concern because of the potential for those deficits to have adverse effects on the lives of the veterans. Primary studies of deployed Gulf War veterans and non-Gulf War-deployed veterans, however, have not demonstrated differences in cognitive and motor measures as determined with neurobehavioral testing. But studies of returning Gulf War veterans with at least one commonly reported symptom (fatigue, memory loss, confusion, inability to concentrate, mood swings, somnolence, gastrointestinal distress, muscle and joint pain or skin or mucous-membrane complaints) demonstrated poorer performance on cognitive tests than by returning Gulf War veterans who did not report such symptoms. Most of those studies did not include control groups (or in some cases valid control groups) so it is not possible to determine whether the combination of symptoms and neurocognitive-test decrements is uniquely associated with Gulf War service.

Several studies focused on multisymptom-based medical conditions: fibromyalgia, CFS, and MCS. Those conditions have several features in common: they do not fit a precise diagnostic category; case definitions are symptom-based (supplemented, in the case of fibromyalgia, by report of pain on digital palpation of tender points in a physical examination); there are no objective criteria independent of patient reports, such as laboratory test results, for validating the case definitions; and the symptoms among those syndromes are to some extent overlapping. Gulf War-deployed veterans report higher rates of symptoms that are consistent with the case definitions of MCS, CFS, and fibromyalgia.

Several large or population-based studies of Gulf War veterans found, by questionnaire, that the prevalence of MCS-like symptoms ranged from 2% to 6%. However, no two of the primary studies used the same definition of MCS, so it is difficult to compare them, and none performed medical evaluations to exclude other explanations, as would be required by the case definition of MCS.

The prevalence of CFS among Gulf War veterans is highly variable from study to study; most studies used the Centers for Disease Control and Prevention case definition. One primary study demonstrated a higher prevalence of CFS in deployed than in nondeployed veterans (1.6% vs 0.1%). Secondary studies also showed a higher prevalence of CFS and CFS-like illnesses among veterans deployed to the Persian Gulf than in to their counterparts who were not deployed or who were deployed elsewhere.

The diagnosis of fibromyalgia is based on symptoms and a very limited physical examination that consists of determining whether pain is elicited by pressing on several points on the body; there are no laboratory tests with which to confirm the diagnosis. Only one of the available cross-sectional studies included both Gulf War-deployed and -nondeployed veterans and used the full American College of Rheumatology case definition of fibromyalgia, including the physical-examination criteria. It found a statistically significant difference in prevalence of fibromyalgia between deployed and nondeployed veterans (2.0% vs 1.2%). Other studies using a case definition based on symptoms alone reported inconsistent results.

Other symptoms that are self-reported more often by deployed veterans are gastrointestinal symptoms, particularly dyspepsia; dermatologic conditions, particularly atopic dermatitis and warts; and joint pains.

There were many reports of gastrointestinal symptoms in Gulf War-deployed veterans. Those symptoms seem to be linked to reports of exposures to contaminated water and burning of animal waste in the war theater. The committee notes that several studies reported a higher rate of self-reported dyspepsia in deployed Gulf War veterans than in nondeployed veterans. In the context of nearly all symptoms being reported more frequently for Gulf War veterans, it is difficult to interpret those findings.

For dermatologic conditions, a few studies have included an examination of the skin and thus would be more reliable than self-reports. Those studies have reported that a few unrelated skin conditions occurred more frequently among Gulf War-deployed veterans; however, the findings are not consistent. From one study that did conduct a skin examination, there is some evidence of a higher prevalence of two distinct dermatologic conditions, atopic dermatitis and verruca vulgaris (warts), in Gulf War-deployed veterans.

Arthralgias (joint pains) were more frequently reported among Gulf War veterans. Likewise, self-reports of arthritis were more common among those deployed to the gulf. Again, in the context of global reporting increases, such data are difficult to interpret. Moreover, studies that included a physical examination did not find evidence of an increase in arthritis.

Finally, Gulf War veterans consistently have been found to suffer from a variety of psychiatric conditions. Two well-designed studies using validated interview-based assessments reported that several psychiatric disorders, most notably PTSD and depression, are 2-3 times more likely in Gulf War -deployed than in nondeployed veterans. Moreover, comorbidities were reported among a number of veterans, with co-occurrence of PTSD, depression, anxiety, or substance abuse. Most of the additional studies administered well-validated symptom questionnaires, and the findings were remarkably similar: an overall increase by a factor of 2-3 in the prevalence of psychiatric disorders.

Outcomes with Objective Measures or Diagnostic Medical Tests

A number of studies examined rates of injuries in Gulf War veterans. Those studies provide evidence of a modest increase in transportation-related injuries and deaths among deployed than among non-deployed Gulf War veterans in the decade immediately after deployment. However, studies with longer followup indicate that the increased injury rate was restricted to the first several years after the war.

With regard to all causes of hospitalization, studies provide some reassurance that excess hospitalizations did not occur among veterans of the Gulf War who remained on active duty through 1994, inasmuch as it has been noted that Gulf War veterans who left the military reported worse health outcomes than those who remained. Those studies, however, are limited by their inability to capture hospitalizations from illnesses that might have longer latency, such as some cancers. In addition, hospitalization data on people separated from the military and admitted to nonmilitary (Department of Veterans Affairs [VA] and civilian) hospitals or those who used outpatient facilities might be incomplete.

Veterans are understandably concerned about increases in cancer, and the studies reviewed did not demonstrate consistent evidence of increased overall cancer in the Gulf War veterans compared with nondeployed veterans. However, many veterans are young for cancer diagnoses, and, for most cancers, the time since the Gulf War is probably too short to expect the onset of cancer. Incidence of and mortality from cancer in general and brain and testicular cancer in particular have been assessed in cohort studies. An association of brain-cancer mortality with possible nerve-agent exposure was observed in one study, but however, there were many uncertainties in the exposure model used. Results for testicular cancer were mixed: one study concluded that there was no evidence of an excess risk, and another, small registry-based study suggested that there might be an increased risk.

Another concern for veterans has been whether ALS is increased in Gulf War veterans. Two primary studies and one secondary study found that deployed veterans appear to be at increased risk of for ALS. One primary study that had the possibility of underascertainment of cases in the nondeployed population was confirmed by a secondary analysis that documented a nearly 2-fold increase in risk. A secondary study that used general population estimates as the comparison group found a slightly higher relative risk.

Peripheral neuropathy has been studied in Gulf War veterans. One large, well-designed study conducted by VA which used a thorough and objective evaluation and a stringent case definition, did not find evidence of excess peripheral neuropathy. Several other secondary studies supported no excess risk. Thus, there does not appear to be an increase in the prevalence of peripheral neuropathy in deployed vs nondeployed veterans, as defined by history, physical examination, and electrophysiologic studies.

With regard to cardiovascular disease, primary studies found no significant differences between deployed and nondeployed veterans in rates of hypertension. One study did report a small but significant increase in hospitalizations due to cardiovascular disease among a subset of deployed veterans who were possibly exposed to the Khamisiyah plume compared with Gulf War-deployed veterans who were not in the suspected exposure area. The increased hospitalizations were due entirely to an increase in cardiac dysrhythmias. In secondary studies, deployed veterans were generally more likely to report hypertension and palpitations, but those reports were not confirmed with medical evaluations. Thus, it does not appear that there is a difference in the prevalence of cardiovascular disease or diabetes between deployed Gulf War veterans and nondeployed.

Many veterans are understandably concerned about the possibility of birth defects in their offspring. Two primary studies yielded some evidence of increased risk of birth defects among offspring of Gulf War veterans. However, the specific defects with increased prevalence (cardiac, kidney, urinary tract, and musculoskeletal abnormalities) in the two studies were not consistent. Overall, the studies are difficult to interpret because of the relative rarity of specific birth defects, use of small sample, timing of exposure (before or after conception), and whether the mother or the father was exposed. There was no consistent pattern of one of more birth defects with a higher prevalence in the offspring of male or female Gulf War veterans. Only one set of defects (that is, urinary tract abnormalities) has been found to be increased in more than one well-designed study. With regard to other adverse reproductive outcomes, the results of one primary study, which had hospital discharge data available, were suggestive of an increased risk of spontaneous abortions and ectopic pregnancies in Gulf War veterans.

Numerous studies in several countries examined respiratory outcomes related to deployment to the Gulf War Theater. The overwhelming majority of studies conducted among Gulf War veterans, whether from the United States, the UK, Canada, Australia, or Denmark, have found that several years after deployment, those deployed report higher rates of respiratory symptoms and respiratory illnesses than nondeployed troops. However, in all five studies, representing four distinct cohorts from three countries (the United States, Australia, and Denmark) that examined associations of Gulf War deployment with pulmonary-function measures or respiratory disease diagnoses based in part on such measures, such associations were not found. The uniformity of the findings is striking, especially given that the same five studies found that Gulf War deployment status was significantly associated with self-reports of respiratory symptoms among three of the four cohorts.

Whereas the studies discussed above examined respiratory outcomes associated simply with deployment vs nondeployment, other studies examined respiratory outcomes associated with specific environmental exposures experienced by Gulf War veterans, including exposure to oil-well fires and nerve agents. The methodologically strongest such study used objective exposure measures and methods and found significant associations between exposure to oil-well fire smoke and a doctor-assigned diagnosis of asthma in veterans. However, the strongest study was limited by the self-selection of participants. A second study, which had the advantage of being population-based, had the key limitation that case definitions were purely symptom-based, and it did not find associations between the same objective measures of exposure to oil-well fire smoke and asthma symptoms. A third study found no significant associations between the same objective measures of exposure to smoke from oil-well fires and later hospitalization for asthma, acute bronchitis, chronic bronchitis, or emphysema; however, the participants were all active-duty veterans, and young adults are seldom hospitalized for those diagnoses, so most cases would not be expected to be captured.

With regard to modeled exposure to nerve agents at Khamisiyah, one study found a small increase in postwar hospitalization for respiratory system disease. However, limitations of that study include probable substantial exposure misclassification based on Department of Defense (DOD) exposure estimates that were later revised, lack of control for tobacco-smoking, lack of a clear dose-response pattern, and low biologic plausibility for this target organ system in a setting in which no effect on nervous system diseases was seen. A second study using revised DOD exposure estimates found no associations between pulmonary-function measures and exposure to nerve agents at Khamisiyah.

RECOMMENDATIONS

The adequacy of the government's response has been both praised and criticized, VA and DOD have expended enormous effort and resources in attempts to address the numerous health issues related to the Gulf War veterans. The information obtained from those efforts, however, has not been sufficient to determine conclusively the origins, extent, and potential long-term implications of health problems potentially associated with veterans' participation in the Gulf War. The difficulty in obtaining meaningful answers, as noted by numerous past Institute of Medicine committees and the present committee agrees, is due largely to inadequate predeployment and postdeployment screening and medical examinations, and lack of monitoring of possible exposures of deployed personnel.

Predeployment and Postdeployment Screening

Predeployment and postdeployment data-gathering needs to include physician verification of data obtained from questionnaires so that one could have confidence in baseline and postdeployment health data. Collection and archiving of biologic samples might enable the diagnosis of specific medical conditions and provide a basis of later comparison. Meticulous records of all medications, whether used for treatment or prophylactically, would have improved the data and their interpretation in many of the studies reviewed.

Exposure Assessment

Environmental exposures were usually not assessed directly, and that critically hampers the assessment of the effects of specific exposures on specific health outcomes. There have been detailed and laudable efforts to simulate and model exposures, but those efforts have been hampered by lack of the input data required to link the exposure scenarios to specific people or even to specific units or job categories. Moving beyond the current state requires that more detailed information be gathered during future military deployments. Specifically, working toward the development of a job-task-unit-exposure matrix in which information on people with specific jobs or tasks or attached to specific units (according to routinely available records) is linked to exposures by expert assessment or simulation studies would enable quantitative assessment of the effects of specific exposures.

Surveillance for Adverse Outcomes

The committee noted that several health outcomes seemed to be appearing with higher incidence or prevalence in the Gulf War-deployed veterans. For those outcomes, the committee recommends continued surveillance to determine whether there is actually a higher risk in Gulf War veterans. Those outcomes are cancer (particularly brain and testicular), ALS, birth defects (including Goldenhar syndrome and urinary tract abnormalities) and other adverse pregnancy outcomes (such as, spontaneous abortion and ectopic pregnancy), and postdeployment psychiatric conditions. The committee also recommends that cause-specific mortality in Gulf War veterans continue to be monitored. Although there was an increase in mortality in the first few years after the Gulf War, the deaths appear to have been related to transportation injuries.

BRIEF SUMMARY OF FINDINGS AND RECOMMENDATIONS

Outcomes Based Primarily on Symptoms or Self-Reports

- No unique syndrome, unique illness, or unique symptom complex in deployed Gulf War veterans. Veterans of the Gulf War report higher rates of nearly all symptoms or sets of symptoms than their nondeployed counterparts; 29% of veterans meet a case definition of "multisymptom illness", as compared with 16% of nondeployed veterans.
- Multisymptom-based medical conditions reported to occur more frequently among deployed Gulf War veterans include fibromyalgia, chronic fatigue syndrome, and multiple chemical sensitivity (MCS).
- Deployment places veterans at increased risk for symptoms that meet diagnostic criteria for a number of psychiatric illnesses, particularly post traumatic stress disorder (PTSD), anxiety, depression, and substance abuse. In addition, co-morbidities were reported among a number of veterans, with PTSD, depression, anxiety, and/or substance abuse.
- Studies of deployed Gulf War veterans vs non-Gulf War deployed have not demonstrated differences in cognitive and motor measures as determined through neurobehavioral testing.
- Studies of returning Gulf War veterans with at least one of the symptoms most commonly reported by Gulf War veterans (i.e., fatigue, memory loss, confusion, inability to concentrate, mood swings, somnolence, GI distress, muscle and joint pain, skin/mucous membrane complaints) found poorer performance on cognitive tests when compared to returning Gulf War veterans who did not report such symptoms.
- Other symptoms that appear to be self-reported more often by deployed veterans are gastrointestinal symptoms, particularly dyspepsia; dermatologic conditions, particularly atopic dermatitis and warts; and joint pains (arthralgias).

Outcomes with Objective Measures or Diagnostic Medical Tests

- Studies of mortality provide evidence for a modest increase in transportation-related injuries and mortalities among deployed compared to non-deployed Gulf War veterans in the decade immediately following deployment. However, studies with longer followup indicate that the increased injury rate was likely to have been restricted to the first several years after the war.
- With regard to all-causes of hospitalization, excess hospitalizations did not occur among veterans of the Gulf War who remained on active duty through 1994. However, Gulf War veterans who left the military reported worse health outcomes than those who remained.
- The studies do not demonstrate consistent evidence of increased overall cancer in the Gulf War veterans compared to nondeployed veterans. Studies of testicular cancer produced inconsistent results, but the latency period for many cancers may not have been reached among Gulf War veterans.
- Studies indicate that Gulf War veterans might be at increased risk for amyotrophic lateral sclerosis (ALS).
- There does not appear to be an increase in the prevalence of peripheral neuropathy in deployed vs non-deployed veterans, as defined by history, physical examination, and electrophysiologic studies.
- It does not appear that there is a difference in the prevalence of cardiovascular disease or diabetes between deployed Gulf War veterans and nondeployed.
- Overall there is no consistent pattern of one of more birth defects with a higher prevalence for the offspring of male or female Gulf War veterans. Only one set of defects, urinary tract abnormalities, has been found to be increased in more than one well-designed study.
- Respiratory symptoms are strongly associated with Gulf War deployment when using comparison groups of non-deployed veterans in most studies addressing this question. However, studies with objective pulmonary function measures find no association between respiratory illnesses with Gulf War deployment across the four cohorts in which this has been investigated.

Specific Gulf War Exposures

Outcomes with Objective Measures or Diagnostic Medical Tests

- Among studies that examined pulmonary outcomes in associations with specific exposures in the Gulf War Theater, exacerbation of asthma associated with oil-well fire smoke has been indicated.
- With respect to nerve agents at Khamisiyah, no study using objective estimates of exposure has found associations with pulmonary function measures or physician-diagnosed respiratory disease. Another study indicated that there might be an increase in brain cancer among such veterans, however, the exposure models are highly uncertain.

RECOMMENDATIONS

- Pre- and post-deployment screening of health status
- Assessment of exposures
- Surveillance for adverse health outcomes, specifically: cancer, ALS, birth defects, adverse pregnancy outcomes, post-deployment psychiatric outcomes, and mortality.