Prevalence of Symptoms and Symptom-based Conditions among Gulf War Veterans: Current Status of Research Findings

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BACKGROUND

Shortly after the end of the Gulf War in March 1991, media reports began to emerge that veterans were experiencing a variety of medically unexplained symptoms, including fatigue, headache, aches and pains, and cognitive disturbances. In January 1992, the press reported an “outbreak” of unexplained symptoms among members of the 123rd Army Reserve Unit in Indiana. Soon, other veterans reported similar symptoms, and public concern grew regarding a “mystery illness” or “Gulf War syndrome.” Subsequent investigation of the reserve unit found no evidence for an outbreak of a unique disease (1). Although, well-defined diseases have been identified among some Gulf War veterans (e.g., 12 cases of viscerotropic leishmaniasis) (2), a substantial proportion of Gulf War veterans’ health complaints involves nonspecific symptoms, which are not readily explained medically.

To address Gulf War veterans’ health concerns, the Department of Veterans Affairs and the Department of Defense established clinical evaluation and registry programs. Although not created for research purposes, these programs have provided useful descriptive information regarding symptoms and illnesses of concern to Gulf War veterans. Analysis of 18,495 Gulf War veterans evaluated by the Department of Defense’s Comprehensive Clinical Evaluation Program found that joint pain, fatigue, headache, memory problems, and sleep disturbance were the most frequently reported symptoms (3). Analysis of 52,835 veterans participating in the Department of Veterans Affairs Gulf War clinical registry found similar results, with fatigue, skin rash, headache, muscle and joint pain, and cognitive problems listed as the most frequent complaints (4). Clinical evaluations have identified medical and psychologic conditions among many veterans reporting for Gulf War registries, although symptomatology remains unexplained in approximately one fifth of these cases. The most common principal diagnoses of registry participants are diseases of the musculoskeletal system and connective tissues; mental disorders; symptoms, signs, and ill-defined conditions; diseases of the respiratory system; and diseases of the skin and subcutaneous tissue (4–6).

The purpose of this review is to document what has been learned about the symptoms and symptom-based conditions reported by Gulf War veterans and the relation between symptoms and exposures. We also describe attempts to develop a case definition for illness among Gulf War veterans.

RESEARCH INVESTIGATIONS OF SYMPTOMATOLOGY AMONG GULF WAR VETERANS AND CONTROLS

Although registry data provide information regarding the occurrence of symptoms among Gulf War veterans, these data do not necessarily reflect the population of Gulf War veterans and do not indicate the frequency with which veterans report symptoms in comparison with other military personnel (7). In 1994, the National Institutes of Health convened a Technology Assessment Workshop to determine, in part, the adequacy of information on unusual illnesses among Gulf War veterans (8). Recommendations from this workshop established the priority of conducting controlled epidemiologic research to determine the preva-
lence of symptoms among Gulf War veterans, and a number of such studies have been completed (9–24) (table 1). This research effort has consisted of population-based studies; cluster and cross-sectional studies of specific military units, commands, or branches of service; and studies of US and other coalition forces. Importantly, control subjects have been assessed in order to compare the prevalence of symptoms and illnesses across groups. These control groups have included military personnel activated during the time of the Gulf War who remained stateside, troops deployed to other regions during the Gulf War, and military participants in other conflicts. Assessment approaches have included mail and telephone surveys, in-person questionnaires and interviews, and physical examinations. The number of respondents participating in these studies has ranged from a few hundred to over 20,000. Response rates have ranged from 31 percent to 76 percent.

The findings of these diverse studies have been remarkably consistent, providing evidence for the validity of these results. Active duty and reserve personnel deployed to the Gulf War self-report nearly all assessed symptoms at a higher rate than comparison groups do. Gulf War veterans are also more likely to rate their overall health status since the Gulf War as poorer than that of their nondeployed peers. The most frequently reported symptoms include fatigue, cognitive difficulties, headaches, myalgia and arthralgia, mood disturbances, and sleep problems. In general, Gulf War veterans are 2–3 times more likely to report these symptoms than are comparison groups. The reported prevalence of symptoms among Gulf War veterans has varied somewhat, reflecting differences in study design, sampling, instruments, and participation rates. Headache, fatigue, cognitive disturbance, pain, and sleep problems have been reported to affect between 15 percent and 50 percent of Gulf War veterans (14, 18, 19, 21, 22). The most useful or generalizable studies of symptom prevalence have been population based, have used a comparable control group of military-era personnel not deployed to the Gulf, and have used at least some standardized or validated instruments to allow comparisons with other populations or studies.

RELATION BETWEEN REPORTED EXPOSURES AND HEALTH OUTCOMES

Several studies have explored the relation between exposures during the Gulf War and subsequent health outcomes; however, this research has been hampered by a lack of objective exposure and health data. Most studies have examined the association between retrospective recall of exposures and self-reported health outcomes, and it is difficult to estimate the effect of recall bias. Large, population-based studies have noted significant associations between most self-reported exposures and multiple health outcomes (11, 18, 19, 24). Studies have also noted associations with specific exposures and adverse health outcomes. For example, Wolfe et al. (15) found that reporting possible exposure to “poison gas” was associated with reporting more symptoms. Nisenbaum et al. (25) found that a belief that biologic or chemical weapons had been used, a reported use of pyridostigmine bromide, or a regular use of insect repellent was associated with illness among Air Force veterans. Haley and Kurt (26) found associations between self-reported exposures to several chemicals and several symptom groups or factors. British investigators (19) found that servicemen who reported receiving multiple vaccines were at increased risk of reporting multiple symptoms. A further analysis showed that receiving multiple vaccines after deployment was associated with reporting multisymptom illness, lower health status, and decreased physical functioning, whereas receiving multiple vaccines prior to deployment was associated with only post-traumatic stress disorder (27). A more recent study of British military personnel found that the number of inoculations, the number of days handling pesticides, and the number of days exposed to smoke from burning oil well fires were related to symptom severity (28).

The time of deployment during the Gulf War has also been examined because several exposures (e.g., use of topical insecticides and pyridostigmine bromide) should vary by season or period of the conflict. Spencer et al. (29) found no differences in the rates of unexplained illness by deployment period. In contrast, Steele (22) found that the prevalence of illness was lowest among Gulf War veterans who departed from the Gulf region prior to January 1991 (before the onset of the air and ground wars), was higher among veterans who departed the region by March 1991, and was highest for those departing in June or July of 1991.

A recently published study of 3,831 Gulf War veteran Seabees (24) defined a medical diagnosis of chronic fatigue syndrome, post-traumatic stress disorder, multiple chemical sensitivity, irritable bowel syndrome, or self-reporting 12 or more of 33 problems as a case of Gulf War illness. Using this outcome, risk factor examinations of demographic and self-reported exposure data revealed previously reported Gulf War illness associations, such as female gender and reserve status, but only weakly implicated individual war exposures. The authors concluded that the aggregate stressors of war were more likely than the specific Gulf War deployment exposures to be a cause of increased symptoms among Gulf War veterans.

As this literature indicates, our understanding of the relation between specific Gulf War exposures and health outcomes is limited by a number of methodological issues and conflicting study findings. Independent review committees who have examined the data have been unable to attribute Gulf War veterans’ symptoms to exposure to any particular stimulus or agent (30–32). Deployment to the Gulf (i.e., exposure to the stress of war) comprises the only consistently identified risk factor for illness among Gulf War veterans.

SYMPTOM-BASED CONDITIONS

Health concerns of Gulf War veterans have been characterized by chronic symptoms that share a number of features with other symptom-based illnesses, such as chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity. The classification of these conditions is based entirely on self-report of symptoms involving multiple organ systems. There are no characteristic physical signs, laboratory abnormalities, or other objective diagnostic criteria. Chronic
fatigue affects 5–10 percent of the general adult population (33); however, chronic fatigue syndrome, as currently defined, is much less common, with an estimated prevalence in the general adult population of 200–600 people per 100,000 (34). The population prevalence of fibromyalgia is estimated to range from 1 percent to 4 percent (35, 36).

Multiple chemical sensitivity has been reported to affect 0.2 percent of college students (37) and 6 percent of randomly selected California residents (38). Self-reports of chemical sensitivity are more frequent, ranging from 15 percent to 33 percent of those surveyed (39, 40). Considerable overlap exists among the symptoms of chronic fatigue syndrome,

Table 1. Summary of controlled research investigations on symptoms of Gulf War veterans

<table>
<thead>
<tr>
<th>Author(s), year, and reference no.</th>
<th>Population</th>
<th>Survey type</th>
<th>No. of respondents</th>
<th>Response rate (%)</th>
<th>Five most frequent symptoms reported by Gulf War veterans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stretch et al., 1995 (9)</td>
<td>Active duty and reserve personnel assigned to Army, Navy, Air Force, and Marine units in Hawaii and Pennsylvania</td>
<td>Anonymous questionnaire distributed at the unit level</td>
<td>4,334</td>
<td>31</td>
<td>Headaches Sinus troubles Head colds Aching joints/bones Sore throat</td>
</tr>
<tr>
<td>Sostek et al., 1996 (10)</td>
<td>Members of a single National Guard unit</td>
<td>Questionnaire</td>
<td>101</td>
<td>74</td>
<td>Fatigue Joint pains Loose or frequent stools Excessive gas Abdominal pain</td>
</tr>
<tr>
<td>Iowa Persian Gulf Study Group, 1997 (11); Doebbeling et al., 2000 (12)</td>
<td>Military personnel who listed Iowa as home of record and served in regular military or activated National Guard or reserve during the period of Operation Desert Shield or Operation Desert Storm</td>
<td>Telephone survey</td>
<td>3,696</td>
<td>76</td>
<td>Feeling tired Multiple joint pains/aches Lack of energy Need to rest more Muscle pain</td>
</tr>
<tr>
<td>Pierce, 1997 (13)</td>
<td>Stratified random sample of women who served in the US Air Force on active duty or were active members of the National Guard or reserve during the period of Operation Desert Shield or Operation Desert Storm</td>
<td>Mail survey administered 2 and 4 years after the war</td>
<td>484 (time 1) 456 (time 2)</td>
<td>76† (time 1) 71† (time 2)</td>
<td>Author does not provide frequency data for individual symptoms but describes a cluster of health problems including skin rashes, depression, cough, weight loss, insomnia, and difficulties with memory</td>
</tr>
<tr>
<td>Fukuda et al., 1998 (14)</td>
<td>Members of two Air National Guard units, an Air Force reserve unit, and an active duty Air Force base located in Florida and Pennsylvania</td>
<td>In-person anonymous questionnaire</td>
<td>3,723</td>
<td>60.5†</td>
<td>Sinus congestion Headache Fatigue Joint pain Difficulty remembering/ concentrating</td>
</tr>
<tr>
<td>Wolfe et al., 1998 (15)</td>
<td>Cohort of 2,949 US Army personnel who returned from the Gulf War through Ft. Devens, Massachusetts, and were first surveyed in 1991; resurveyed in 1992–1993</td>
<td>Mail survey</td>
<td>2,313</td>
<td>78</td>
<td>Aches/pains Lack of energy or fatigue Headaches Insomnia Feeling nervous or tense</td>
</tr>
<tr>
<td>Proctor et al., 1998 (16)</td>
<td>Stratified random sample of members from the Ft. Devens Gulf War cohort (US Army active, reserve, and National Guard); the New Orleans Gulf War cohort (represents all services’ active, reserve, and National Guard); and members of a Maine National Guard unit from an air ambulance company deployed to Germany (time 3 assessment)</td>
<td>In-person questionnaires, neuropsychologic testing, psychiatric interviews</td>
<td>343</td>
<td>53† 62 (Devens cohort)</td>
<td>Difficulty concentrating Joint pains Headaches Inability to fall asleep Backaches</td>
</tr>
<tr>
<td>Goss Gilroy, Inc., 1998 (17)</td>
<td>All Canadian Gulf War veterans; Canadian forces who served elsewhere during the time of the Gulf War</td>
<td>Mail survey</td>
<td>6,552</td>
<td>64.5</td>
<td>Cognitive dysfunction Depression Fibromyalgia Respiratory disease Alcohol abuse</td>
</tr>
</tbody>
</table>
fibromyalgia, and multiple chemical sensitivity, which may represent different points on a continuum of illness or different manifestations of the same condition (41, 42).

Several studies have assessed chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity among Gulf War veterans. However, it is impossible to generalize from their results. One cross-sectional survey of 41 outpatients from a single Department of Veterans Affairs medical center found that Gulf War veterans who reported poor health were more likely to also report chemical sensitivity than were

TABLE 1. Continued

<table>
<thead>
<tr>
<th>Author(s), year, and reference no.</th>
<th>Population</th>
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<th>Five most frequent symptoms reported by Gulf War veterans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray et al., 1999 (18)</td>
<td>Members of 14 regular active-duty US Navy Seabee commands at Port Hueneme, California, and Gulfport, Mississippi, who served from September 1990 until the time of the survey</td>
<td>In-person questionnaire, clinical specimens, selected physical measurements</td>
<td>1,497</td>
<td>53</td>
<td>Unusual fatigue Forgetfulness Trouble sleeping Sleepy all the time Rash</td>
</tr>
<tr>
<td>Unwin et al., 1999 (19)</td>
<td>British regulars and reservists of the Royal Navy, Army, and Air Force who served between September 1, 1990, and June 30, 1991; military personnel who served in Bosnia between April 1, 1992, and February 6, 1997</td>
<td>Mail survey</td>
<td>8,195</td>
<td>65</td>
<td>Unrefreshing sleep Irritability/outbursts of anger Headaches Fatigue Sleeping difficulties</td>
</tr>
<tr>
<td>Ishoy et al., 1999 (20)</td>
<td>Members of Danish peace-keeping United Nations task force who were stationed in the Persian Gulf area between August 2, 1990, and December 31, 1997; Danish armed forces who served during the time of the Gulf War</td>
<td>Mail survey, interview, health examination</td>
<td>917</td>
<td>75†</td>
<td>Concentration/memory difficulties Abnormal feeling of fatigue Unrefreshing sleep Unusual feeling of fatigue during the day Depression/sadness</td>
</tr>
<tr>
<td>Kang et al., 2000 (21)</td>
<td>All US troops deployed to the Persian Gulf area during the Gulf War; 50% random sample of all troops who were in the military between September 1990 and May 1991 and not deployed to the Persian Gulf</td>
<td>Mail survey, telephone interview with nonrespondents, medical record review</td>
<td>20,917</td>
<td>70</td>
<td>Runny nose Headache Unrefreshing sleep Anxiety Joint pain</td>
</tr>
<tr>
<td>Steele, 2000 (22)</td>
<td>Kansas residents who had served on active military duty for any period between August 1990 and July 1991 and were separated or retired from the military or currently serving in a reserve component</td>
<td>Telephone survey</td>
<td>2,030</td>
<td>65†</td>
<td>Not feeling rested after sleep Pain in joints Fatigue Problems falling/staying asleep Sinus congestion</td>
</tr>
<tr>
<td>Cherry et al., 2001 (23)</td>
<td>All United Kingdom troops deployed to the Gulf or Gulf states between September 1990 and June 1991; random sample of personnel in the military on January 1, 1991, who were not deployed to the Gulf but were eligible for deployment</td>
<td>Self-administered questionnaires (method of administration differed among groups)</td>
<td>12,191</td>
<td>85</td>
<td>Severity rather than frequency of symptom reported</td>
</tr>
<tr>
<td>Gray et al., 2002 (24)</td>
<td>All regular and reserve Navy personnel who served on active duty in Seabee commands for at least 30 consecutive days between August 1, 1990, and July 31, 1991</td>
<td>Mail survey</td>
<td>11,868</td>
<td>63†</td>
<td>Short-term memory problems Unusual fatigue Trouble sleeping Joint pain Joint stiffness</td>
</tr>
</tbody>
</table>

* Method for distributing questionnaire not specified.
† The single response rate list in the table was calculated from information provided in the publication on the total number of eligible subjects and the number of respondents.
‡ Reflects symptom patterns suggestive of a priori identified medical and psychiatric conditions.
healthy Gulf War veterans or ill and healthy era veterans (43). Pollet et al. (44) examined 72 participants in the Department of Veterans Affairs Gulf registry who reported severe fatigue and chemical sensitivity to determine the number that met criteria for chronic fatigue syndrome and multiple chemical sensitivity. Thirty-three were diagnosed as having chronic fatigue syndrome, of which 14 also met criteria for multiple chemical sensitivity. Six veterans satisfied the operational case definition of multiple chemical sensitivity alone; two received a concurrent diagnosis of fibromyalgia. The rate of multiple chemical sensitivity in veterans with chronic fatigue syndrome was not significantly different from that among a sample of nonveterans with chronic fatigue syndrome. In a larger sample of Department of Veterans Affairs registry participants (*n* = 1,161), 16 percent reported symptoms consistent with chronic fatigue syndrome and 13 percent reported symptoms characteristic of multiple chemical sensitivity (45). Thirty-three (3 percent) veterans reported symptoms of both chronic fatigue syndrome and multiple chemical sensitivity.

These symptom-based conditions have also been assessed in several population-based studies of Gulf War veterans. In the study by the Centers for Disease Control and Prevention of four Air Force units, 43 percent of Gulf War veterans and 17 percent of nondeployed personnel reported current fatigue that had lasted 6 months or longer, and eight of 158 (5 percent) clinically evaluated Gulf War veterans met criteria for chronic fatigue syndrome (14). Five percent of the Gulf War veterans reported chemical sensitivity compared with 2 percent of nondeployed personnel. In the Iowa study, chronic fatigue was reported at a lower prevalence than in the Air Force study (1–3 percent of Gulf War veterans and 0.2–1 percent of nondeployed personnel) (11). However, similar to the Air Force study, 5 percent of Gulf War veterans and 3 percent of nondeployed troops in the Iowa study reported chemical sensitivity symptoms (46). Symptoms of fibromyalgia were reported by 18–24 percent of Gulf War veterans and by 9–13 percent of nondeployed personnel who participated in the Iowa study (11). In the Iowa study, multiple chemical sensitivity was defined as reporting illness from chemical sensitivity, reporting sensitivity to two or more of eight categories of substances, having symptoms in at least two organ systems, and manifesting evidence of impairment or behavioral change in response to perceived sensitivity (11). The 169 (4.6 percent) subjects in the Iowa study who met criteria for multiple chemical sensitivity reported medical disability, unemployment, physician and emergency department visits, in-patient hospital stays, and impaired function across a broad range of health domains more often than did subjects without multiple chemical sensitivity (47). In a more recent study of Navy Seabees, Gulf War veterans were significantly more likely to report physician-diagnosed, multisymptom conditions than were their peers who were not deployed to the Persian Gulf (24). Chronic fatigue syndrome was reported by 5.2 percent of Gulf War Seabees, by 0.8 percent of Seabees deployed elsewhere, and by 0.7 percent of nondeployed Seabees. Multiple chemical sensitivity was reported by 1.6 percent of Gulf War Seabees and by 0.3 and 0.4 percent of Seabees deployed elsewhere and nondeployed Seabees, respectively. Similar findings were reported from a study of chemical sensitivity and chronic fatigue among 180 Gulf War veterans from the Devens cohort and 46 veterans deployed to Germany during the Gulf War (48). The number of subjects with symptoms of chemical sensitivity and chronic fatigue was significantly higher among the Gulf War veterans when compared with the Germany-deployed veterans (chemical sensitivity: 14 percent vs. 2 percent; chronic fatigue: 29 percent vs. 9 percent). Gulf War veterans were also more likely than were veterans deployed to Germany to meet criteria for multiple chemical sensitivity and chronic fatigue syndrome; however, the differences were not statistically significant. A presumptive diagnosis of multiple chemical sensitivity and chronic fatigue syndrome was made for 3 percent and 2 percent of the Gulf War veterans, respectively. None of the veterans deployed to Germany met criteria for multiple chemical sensitivity or chronic fatigue syndrome.

Studies of other Gulf War cohorts also indicate that Gulf War veterans are more likely than other veteran groups to report symptom-based conditions. Three percent of United Kingdom Gulf War veterans reported symptoms consistent with chronic fatigue syndrome compared with 0.8 percent of Bosnia veterans and 0.8 percent of Gulf War-era veterans (19). Relatively few United Kingdom subjects reported symptoms of chemical sensitivity (0.8 percent of Gulf War veterans, 0.4 percent of Bosnia veterans, and 0.3 percent of Gulf War-era veterans), and these symptoms were not associated with deployment status. Canadian Gulf War veterans were also more likely than were controls to report symptoms of chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity (17). Among Canadian Gulf War veterans, 9–10 percent reported symptoms of chronic fatigue compared with 2 percent of Gulf War-era controls, 16 percent reported symptoms of fibromyalgia compared with 10–11 percent of controls, and 3 percent reported symptoms of multiple chemical sensitivity compared with 0.5–1 percent of controls.

**CASE DEFINITION**

As with other symptom-based conditions, research into postulated illnesses of Gulf War veterans has been limited because of difficulties in developing a case definition. Approaches for defining other symptom-based conditions, such as chronic fatigue syndrome and fibromyalgia, have relied upon expert panels that developed consensus definitions based on their clinical and research experience (49–51). Research into illnesses among Gulf War veterans has taken a somewhat different approach, relying primarily on statistical, data-driven approaches, primarily factor analysis, for developing working case definitions. Factor analysis is a statistical technique developed for data reduction and for developing scales and identifying otherwise latent relations among multiple variables (52). Haley et al. (53) defined three primary illness constructs among 249 Gulf War veterans from the 24th Reserve Naval Mobile Construction Battalion. These were labeled as “impaired cognition” (characterized by problems with attention, memory and reasoning, insomnia, depression, daytime sleepiness, and
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Sures. Factor analysis identified three symptom factors replicable in random samples of the deployed subjects: “somatic distress” (characterized by joint stiffness, myalgias, polyarthralgia, numbness or tingling, headaches, and nausea); “psychologic distress” (feeling nervous, worrying, feeling distant or cut off, depression, and anhedonia); and “panic” (anxiety attacks; heart racing, pounding, or skipping; attacks of chest pain or pressure; and attacks of sweating). Data from deployed and nondeployed subjects were analyzed separately and demonstrated the same three-factor structure, which explained similar proportions of the common variance in both groups. Additionally, one half (50 percent) of the deployed and 14 percent of the nondeployed troops reported health problems attributed to military service during 1990–1991, comparable with the proportions of Air Force veterans meeting the working definition of chronic multisymptom illness of Fukuda et al. (14).

Factor analysis of symptom data from 524 active duty Navy Seabee Gulf War veterans identified five factors that were labeled as insecurity or minor depression, somatization, depression, obsessive-compulsive, and malaise (56). The insecurity/minor depression, somatization, and obsessive-compulsive factors were consistent with three symptoms’ scales from the Hopkins Symptom Checklist (57) component questions. The depression and malaise factors represented investigator-derived questions relating to symptoms of depression and to symptoms commonly reported by Gulf War veterans (tender or swollen glands/lymph nodes, constipation, fever, sudden hair loss, chills, night sweats, sore throat, and a validity symptom, earlobe pain), respectively. Similar symptom factors were derived from the self-reported symptom data obtained from 935 active duty Navy Seabee nondeployed Gulf War-era veterans (56). The major difference in symptom reporting between Gulf War and nondeployed Seabees was the higher prevalence of symptoms reported by the Gulf War veterans. As with the Iowa, British, and Air Force studies, Gulf War veterans and nondeployed Gulf War-era veterans reported similar patterns or factors of symptoms. Importantly, these four studies did not support the identification of a Gulf War syndrome.

The most recent attempt to use factor analysis to identify a Gulf War-related syndrome was conducted by Kang et al. (58) on symptom data from a population-based sample of Gulf War veterans and their nondeployed peers. The sample included all branches of the service and included active duty, reserve, and National Guard troops. The analysis initially yielded four factors with limited interpretability and no difference between the deployed and nondeployed veterans. These factors were identified as representing respiratory and infectious symptoms, gastrointestinal symptoms, musculoskeletal symptoms, and neurologic, fatigue, and mood symptoms. In a controversial analysis, the authors proceeded to extract additional factors, arriving at a six-factor solution which identified one factor that was present among Gulf War veterans but not among nondeployed veterans. This factor contained a cluster of symptoms of blurred vision, loss of balance or dizziness, tremors or shaking, and speech difficulty. The investigators suggest that this factor may represent neurologic impairment that should be further examined with clinical studies.

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As with other symptom-based conditions, lack of specificity or the ability to rule out alternative medical and psychiatric causes of chronic somatic symptoms has been a major limitation in the development of a specific case definition for illness among Gulf War veterans (59). This has been true of both the expert consensus and the data-driven approaches to case definition development, since both approaches rely on symptom-based screening. Traditionally, when the patient reports the subjective experience of changes in the body that are not explained by a pathologically defined disease or by an objective, observable abnormality in the body, these changes are referred to as “medically unexplained,” “functional,” or “somatization” symptoms. Modern medicine has placed an emphasis on explaining and curing disease by focusing on measurable, objective pathology rather than on describing disease. In the case of Gulf War research, because initial clinical studies have not been able to identify characteristic physical and laboratory abnormalities, an alternative approach of applying quantitative methods, such as factor analysis, was used to define illness. These methods seek to assess the specificity of symptom clusters in particular groups of patients. However, these data-analytic methods are limited in that they do not address issues of biologic plausibility, are dependent upon the initial assessment and inclusion in the analysis of the appropriate symptoms, and involve subjective interpretation of the factors.

RESEARCH LIMITATIONS

Investigating the Gulf War’s health impact has been challenging because of the lack of objective physical findings, a satisfactory specific case definition of illness, and well-documented exposure data. Symptoms of illness among Gulf War veterans involve multisystem complaints without characteristic physical examination or laboratory abnormalities and are similar to symptoms commonly experienced in all adult populations (60, 61). Little progress has been made by the medical community in developing widely accepted diagnostic criteria for many of the symptom-based conditions reported by Gulf War veterans. Additionally, well-documented, easily accessible, baseline health data have not been routinely available on military populations. Thus, self-reported symptom and exposure data have formed the basis of much research concerning the health impact of the Gulf War.

McCauley et al. (62) demonstrated how the reporting of symptoms can vary over time and complicate classification. When symptom reporting on a mailed questionnaire was compared with reporting during clinical evaluation 3 months later, agreement that the symptom was present at both time points was highest for fatigue and cognitive-psychologic symptoms (percentage of agreement ranging from 74 percent to 79 percent) and lowest for musculoskeletal pain, gastrointestinal complaints, and skin rash or lesions (percentage of agreement ranging from 4 percent to 35 percent). Pollet et al. (44) noted that, when veterans who had complaints of severe fatigue or chemical sensitivity were later evaluated clinically, they were found to be substantially less ill than previously reported. Gray et al. (18) also found poor test-retest reliability and low medical and service record validation of self-reported symptom and health history data, whereas there was fair to excellent agreement for questions regarding demographics, health habits, and deployment exposures.

The health impact of the Gulf War has been the focus of considerable media and Congressional attention (31, 63–65). This attention may have increased health concerns among Gulf War veterans and their families. Gray et al. (6) found increased enrollment in the registries of the Department of Defense and the Department of Veterans Affairs during periods of high media attention to Gulf War issues. Increased health concerns may lead to higher levels of reporting of symptoms, illnesses, and exposures because affected individuals may be more attentive to symptoms and will more thoroughly search their memories for environmental events or other potential explanations or causes. McCauley et al. (66) investigated the role of media publicity on reporting exposure information. Although reporting use of insect repellents was related to specific media events, overall there was little or no relation between Gulf War media events between 1995 and 1997 and self-reported exposures. However, veterans in this study often reported exposures that were highly improbable given their dates of service. For example, veterans who did not serve during the combat phase reported exposure to Scud missile alarms and detonations, pyridostigmine bromide, and chemical warfare agents.

There are several other potential sources of bias or systematic error in studies that may influence the validity and generalizability of their results. These include self-referral, differential recall, response, and participation biases. Participation rates are a crucial issue in all survey studies. Reasons for nonparticipation vary: Some subjects cannot be located or interviewed, some may be too ill to participate, or some may refuse for other reasons. If the response rate is low, nonresponse bias may seriously limit the ability to generalize the study’s results. Importantly, studies of Gulf War veterans have had widely varying response rates, ranging from 31 percent to 76 percent. Ill Gulf War veterans may be more likely to participate in studies and more likely to recall health concerns and possible exposures than are others. Conversely, studies of active duty populations may underestimate Gulf War veterans’ health status because ill veterans may not want to provide information out of fear of jeopardizing their military careers. Similarly, studies that do not track subjects regardless of whether they remain on active duty or not are prone to nonparticipation bias, since some veterans may be more likely to leave the military because of their illness.

It is important to note that medically unexplained physical symptoms or those present without objective physical examination or laboratory test abnormalities are remarkably prevalent in the community (59). A population-based survey of four communities found that 32 percent of respondents reported headache, 23 percent reported dizziness, and 25 percent reported fatigue; 31 percent of the symptoms were medically unexplained (61). According to the National Ambulatory Medical Care Survey, physical symptoms accounted for over half of all US ambulatory care visits (67).
Multiple studies demonstrate that medically unexplained physical symptoms are strongly associated with functional impairment or disability, health care utilization, psychosocial distress, and psychiatric disorders (68–73). Assessing psychosocial factors is clearly important when evaluating patients with medically unexplained symptoms. Stressful life events, anxiety and depressive disorders, and childhood and adult trauma have all been found to be associated with multiple physical symptoms (74).

CONCLUSIONS AND FUTURE DIRECTIONS

As this review indicates, considerable progress has been made in documenting the prevalence of symptoms and possible symptom-based conditions among Gulf War veterans in comparison with appropriate control groups. These research efforts have identified a group of medically unexplained physical symptoms, characterized primarily by fatigue, cognition problems, and musculoskeletal complaints. These symptoms share a number of characteristics with other well-described, symptom-based conditions, especially chronic fatigue syndrome and fibromyalgia, and are commonly seen in the general population. Although symptoms are more prevalent among Gulf War veterans than among their nondeployed peers, this pattern of symptoms is not unique to Gulf War service and does not appear to represent a unique illness or “Gulf War syndrome.” In fact, illnesses similar to those affecting Gulf War veterans have been noted among veterans of other military deployments dating back to the US Civil War (75, 76). Research has been hampered by the difficulty of developing case definitions for symptom-based conditions without objective criteria and by the lack of adequate exposure information.

The current government-funded research portfolio contains a number of innovative projects that will build on this initial examination of symptoms among Gulf War veterans (77). This includes research to validate self-reported symptoms among Gulf War veterans, research on case definition issues, research on the possible role of chronic fatigue syndrome, multiple chemical sensitivity, and fibromyalgia, and research on the biologic bases of symptoms such as pain and fatigue. In addition, the relation of central nervous system, immunologic, and neuropsychiatric abnormalities and symptomatology among Gulf War veterans is being explored in a number of studies.

A better understanding of the epidemiology of medically unexplained physical symptoms, the role of predisposing, precipitating, and perpetuating factors, and approaches to the prevention and management of these symptoms would assist in addressing health outcomes associated with future deployments. Simultaneous efforts must be made to improve environmental and health surveillance and medical record keeping during deployments. The lack of timely and objective information regarding potential exposure to environmental hazards contributed to the anxiety associated with deployment to the Gulf War and hampered our ability to respond to Gulf War veterans’ health concerns.

REFERENCES

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