Gulf War Illness Symptom Severity and Onset: A Cross-Sectional Survey

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ABSTRACT  Introduction: Gulf War illness (GWI) affects 25 to 32% of the 693,826 veterans of the First Persian Gulf War. The etiology and pathophysiology of GWI remain controversial, but the condition is attributed to toxic exposures and stress in the deployed setting. The Kansas criteria used for GWI diagnosis highlight 37 symptoms that were more prevalent in deployed compared to nondeployed veterans. This study employed the Kansas criteria to identify recent symptom severity, assess the perceived burden of disease for veterans with GWI, and characterize disease course over the past three decades. Materials and Methods: The Kansas criteria were operationalized into a questionnaire to provide a summary of symptom severity, approximate year of onset, and an aid for diagnosis. The online version of the questionnaire was completed by 485 veterans with GWI. Symptom data were grouped for analysis based on observed trends. This study received approval from the Georgetown University Institutional Review Board (IRB 2018–0430). RESULTS: Symptom severity for the past 6 months demonstrated a high burden of disease for veteran participants. Frequency analysis of total severity scores (out of 148) showed a unimodal distribution with a median score of 95 (1st quartile = 78, 3rd quartile = 110), minimum score of 19, and maximum of 146. Over 89% of respondents had moderate or severe fatigue, sleep disturbances, pain, and abdominal symptoms over the past 6 months. The veterans who participated in this study reported cumulative frequencies higher than those in a meta-analysis of 21 GWI large epidemiologic cross-sectional studies for symptoms around 1998. The cumulative frequency of symptoms indicated long duration of symptoms, although recall bias must be taken into consideration. Conclusions: This cross-sectional sample of self-selected veterans with GWI demonstrates a high current burden of disease and reveals symptom onset patterns. The information from this study can be used to better understand the long-term trajectory of GWI and be integrated into the treatment and diagnosis of impacted veterans. It can also be used as historical deployed health data and inform the future medical care of combat veterans experiencing health effects from war exposures.

INTRODUCTION

Decades after Operations Desert Storm and Shield, veterans of the First Persian Gulf War (1990–1991) continue to battle debilitating and persistent medical problems. Gulf War illness (GWI) is the flagship of these health concerns, affecting 25 to 32% of the 693,826 men and women who were deployed in this conflict.1 GWI—also referred to as Gulf War syndrome, Persian Gulf Syndrome, and Chronic Multisystem Illness—is a poorly understood disorder with an expansive range of symptoms, among which chronic fatigue, pain, and neurologic disturbances predominate. The etiology and pathophysiology of GWI remain controversial despite years of investigations into many confirmed toxic exposures including organophosphate pesticides, sarin nerve agents, pyridostigmine bromide prophylaxis, combustion products and fuels, and depleted uranium, among others.2 Complex interactions with additional deployment-related stressors including combat exposure, poor living conditions, and discomfort with the physical desert environment may have contributed as a “Gulf War Stressor State.” The U.S. Department of Veterans Affairs (VA) recognizes that, “certain chronic, unexplained symptoms existing for six months or more are related to Gulf War service without regard to cause.”3 Despite the evidence for GWI, affected veterans have often been told by medical providers that they suffer from psychosomatic illness or that their ailment is “all in their heads.”4,5

In the years following the war, a number of studies focused on comparing the unusual medical plights of combat veterans to their nondeployed counterparts. The Kansas Criteria are the most recently developed standards used to diagnose GWI, comprising 37 symptoms shown to be more prevalent among deployed versus nondeployed cohorts (Table S1).4,5 The symptoms are divided into six domains: cognitive and sleep, pain, neurologic and cognitive, respiratory, gastrointestinal, and skin, plus an “other” category. Veterans must experience moderate-to-severe symptoms in at least three of the six core domains for a GWI diagnosis. Many cross-sectional epidemiological studies have been conducted to establish symptom prevalence; however, there is limited information...
about the incidence and progression of symptom development over the past three decades.4,6–10

The objectives of this study were to assess (1) symptom severity over the past 6 months, (2) disease course based on recalled symptom onset, and (3) veterans’ perceived burden of disease. Though the strong effect of recall bias is inherent in all history-based medical inquiries, the symptom severity and recalled onset data from this study can be used as a self-referential impression of disease burden for individuals. The high level of morbidity among veterans with GWI may encourage further investigations of the underlying disease mechanism and potential treatment options, as well as increase the recognition of GWI as a valid diagnosis in general clinical practice. Identified patterns of symptom development can be integrated into medical providers’ ongoing surveillance of veterans with GWI and assist with discriminating it from other disease mechanisms in an aging population. Finally, GWI disease course data can serve as a historical reference for health effects from war exposures, potentially informing the management of combat veterans’ health following hazardous occupational exposures from other conflicts.

METHODS

The protocol for this study was approved by the Georgetown University Institutional Review Board. GWI veterans from the First Persian Gulf War were recruited from August to December 2018 via email and social media posts to Gulf War veteran groups and GWI patient groups. Interested participants (n = 540) were directed to a website where written consent was required before proceeding to the questionnaire. Demographic information including gender, age, race, ethnicity, smoking status, and VA disability coverage was collected. Two participants declined written consent (n = 538). Fifteen participants were excluded for reporting age less than the 40 to 49 years bracket as these veterans would not have been participants were excluded for reporting age less than the 40 years bracket as these veterans would not have been eligible to deploy during the First Persian Gulf War (n = 523). Completed questionnaires were screened to ensure remaining veterans met the Kansas criteria for GWI by reporting multiple or moderate-to-severe scores in three of six symptom domains: fatigue/sleep, pain, neurologic/cognitive/mood, gastrointestinal, respiratory, and skin (n = 485). Race and ethnicity were self-reported within the options defined by the investigators.

Symptom Severity

Veterans graded the severity of the 37 Kansas Criteria symptoms over the past 6 months on a 5-point anchored ordinal grading scale: none (0), trivial (1), mild (2), moderate (3), or severe (4). Total Kansas criteria scores were calculated by adding the scores for all 37 criteria together. Frequency analysis was performed to examine overall morbidity. Levels of symptom severity in the past six months were plotted as the percentage of the group (n = 485) with none, trivial, mild, moderate, or severe complaints.

Symptom Onset

Veterans reported their best recollection for year of symptom onset and whether each symptom began in theatre. The cumulative frequency of each symptom was plotted over year of onset. Years of onset were grouped to minimize recall bias and included onset in theatre from 1990 to 1991, shortly after the Gulf War from 1992 to 1994, and then 5-year increments following. Symptom severity at the time of onset was not recorded due to the potential for recall bias.

Symptoms were grouped according to observed long-term trends, diverging from the six Kansas criteria domains established in 2000. The newly formed groups, nine in total, include fatigue and sleep, pain, neurologic and cognitive, sensory 1, sensory 2, abdominal, airway, epithelial, and mood. The fatigue and sleep, pain, and abdominal (gastrointestinal) groupings remained the same as in the original Kansas Criteria. Mood symptoms were separated out from neurologic and cognitive symptoms. The “sensory 1” group includes light sensitivity, headaches, tinnitus, sinus congestion, and hearing loss. The “sensory 2” group includes temperature sensitivity, dizziness, response to chemicals, and night sweats. The airway group combined respiratory symptoms of sore throat and swollen lymph nodes in neck. The epithelial group combined skin rash with problems with teeth or gums, mouth sores, unusual hair loss, and self or partner having a burning sensation after sex.

Cumulative frequencies were compared to a recent meta-analysis of cross-sectional epidemiological studies reporting the prevalence of Kansas Criteria or similar complaints among Gulf War veterans.11 Point prevalence found in three or more publications were plotted on the cumulative frequency graphs to assess the validity of the data in this study. The prevalence of veterans experiencing moderate-or-severe symptoms in the past 6 months was plotted as well to compare cumulative frequency trends to current morbidity.

Additional Measures

Potential comorbid conditions with overlapping diagnostic criteria were measured for generalized anxiety disorder (GAD), chronic fatigue syndrome (CFS), and post-traumatic stress disorder (PTSD). The GAD-7 questionnaire was used to assess for GAD, rating the frequency of seven symptoms over the past 2 weeks as “not at all” (0), “several days” (1), “more than half the days” (2), and “nearly every day” (3), with scores greater than 10 required for diagnosis.12 A previously validated questionnaire based on the 1994 Fukuda criteria was used for CFS. Symptom severity over the past 6 months was scored as 0 (none), 1 (trivial), 2 (mild), 3 (moderate), and 4 (severe), and the following criteria must have been met for CFS diagnosis: (1) fatigue severity had to be moderate or severe, (2) at least four of the other eight ancillary criteria had to be moderate or severe, (3) the sum of the eight ancillary criteria scores had to be ≥14 (range 0–32).13–15

PTSD diagnosis was self-reported along with
the year of diagnosis. Veterans also were asked about their frequency of pain medication use and if they had ever been hospitalized for substance abuse or a psychiatric problem. Finally, veterans were asked whether they had ever been told by a medical provider if their symptoms were “all in their head.”

RESULTS

Demographics

The study population comprised 392 men and 93 women (n = 485). Veterans were mainly between the ages of 50 to 59 (51.3%) and 40 to 49 (38.1%). The majority of veterans identified as White (81.7%) and not Hispanic or Latino (86.2%). VA disability benefits were reported by 77.9% (Table I).

Symptom Severity

Total symptom scores (out of 37) for the past 6 months, calculated by adding 1 point for each symptom of the Kansas Criteria, reflected a high level of morbidity averaging 32.4 ± 4.7 (Table II). Frequency analysis of total severity scores (out of 148) showed a unimodal distribution with a median score of 95 (first quartile = 78, third quartile = 110), minimum score of 19, and maximum of 146.

Some groups of symptoms demonstrated similar distributions of severity scores (Figure 1). Fatigue and sleep symptoms were severe in 33 to 57% of the cohort; pain was severe in 33 to 48%. Abdominal complaints were predominantly moderate (32 to 35%). Cognitive and mood symptoms, including memory problems, difficulty concentrating, paresthesias, and symptomatic response to chemicals and odors, were moderate or severe in 69 to 78%. Others, including tremors and blurred vision, were moderate or severe in 37 to 47%. Oral and airway, sensory, and other symptoms showed a wider range of severity. More than 89% of veterans reported having experienced every measured fatigue, pain, and abdominal symptom within the last six months.

Symptom Onset

Visual inspection of curves of cumulative frequency versus year of onset for each symptom revealed several patterns and subgroups of symptoms (Figure 2). The following cutoffs were chosen to evaluate groups of symptom onset: early onset (cumulative frequency >20% by 1992), intermediate onset (>40% between 1992 and 1994), and delayed onset (>40% after 1995). Point prevalence data from published studies were lower than the cumulative frequencies for all symptoms.

Early Onset Symptoms

All abdominal, certain sensory (headaches, tinnitus, hearing loss, and sinus congestion), and rash symptoms were reported by more than 20% of veterans in theatre. Fatigue, problems falling or staying asleep, not feeling rested after sleep, dyspnea, and persistent cough were also reported by more than 20% of veterans at that time. Tinnitus was the only symptom reported more than 30% of veterans in theatre. All 37 symptoms were reported by at least 8% of veterans in theatre.

Intermediate Onset

In 1992–1994, more than 40% of veterans reported every measured fatigue/sleep, pain, mood, and abdominal symptom. All 37 symptoms were reported by at least 26% of veterans. “Feeling down or depressed” and “feeling irritable or angry outbursts” had parallel trajectories.

| TABLE I. Demographics of Participating Veterans With Gulf War Illness |
|---------------------------------------------------------------|
| Demographic               | N (%)               |
| Gender                   |                     |
| Male                      | 392 (80.8)          |
| Female                    | 93 (19.2)           |
| Age                       |                     |
| 40–49                     | 185 (38.1)          |
| 50–59                     | 249 (51.3)          |
| 60–69                     | 48 (9.9)            |
| 70–75                     | 3 (0.6)             |
| Ethnicity                 |                     |
| Hispanic or Latino        | 38 (7.8)            |
| Not Hispanic or Latino    | 418 (86.2)          |
| Did Not/Prefer Not to Answer | 29 (6.0) |
| Race                      |                     |
| American Indian or Alaskan Native | 9 (1.9) |
| Asian                     | 1 (0.2)             |
| Black or African American  | 32 (6.6)            |
| Native Hawaiian or Pacific Islander | 2 (0.4) |
| White                     | 396 (81.7)          |
| More than 1 Race          | 22 (4.5)            |
| Did Not/Prefer Not to Answer | 23 (4.7) |
| Education                 |                     |
| Less than high school     | 1 (0.2)             |
| High school/GED           | 73 (15.1)           |
| Some college              | 224 (46.2)          |
| College degree            | 148 (30.5)          |
| Master’s degree and beyond| 39 (8.0)            |
| Smoking status            |                     |
| Currently smoking         | 101 (20.8)          |
| Quit within the past 6 months | 20 (4.1) |
| Quit more than 6 months ago | 158 (32.6)         |
| Never smoked              | 204 (42.1)          |
| Did not/prefer not to answer | 2 (0.4)            |
| Benefits program enrollment|                  |
| VA disability             | 378 (77.9)          |
| Social security           | 127 (26.2)          |
| Disability                | 106 (21.9)          |
| Worker’s compensation     | 5 (1.0)             |

Demographic data for this population of Gulf War veterans reflect participation by predominantly male, white, and not Hispanic or Latino military personnel. Most participants were aged 50 to 59 years and had the education level of at least some college. The majority of veteran participants (77.9%) had VA disability benefits.
TABLE II. Gulf War Illness Symptom Severity Scores for the Past 6 Months Grouped According to Observed Trends

| Domain and Symptom                  | Mean ± SD, N = 485 |
|-------------------------------------|--------------------|
| Fatigue and sleep                   |                    |
| Not feeling rested after sleep      | 3.49 ± 0.71        |
| Fatigue                             | 3.41 ± 0.69        |
| Problems falling or staying asleep  | 3.28 ± 0.98        |
| Feeling unwell after exercise or exertion | 2.98 ± 1.02 |
| Pain                                |                    |
| Body pain                           | 3.14 ± 0.89        |
| Joint pain                          | 3.38 ± 0.76        |
| Muscle pain                         | 3.15 ± 0.81        |
| Neurologic and cognitive            |                    |
| Memory                              | 3.19 ± 0.91        |
| Concentration                       | 3.15 ± 0.87        |
| Word finding                        | 2.94 ± 1.01        |
| Numbness                            | 3.00 ± 1.06        |
| Blurred vision                      | 2.29 ± 1.22        |
| Tremors                             | 2.00 ± 1.29        |
| Sensory 1                           |                    |
| Light sensitivity                   | 2.66 ± 1.23        |
| Headaches                           | 2.79 ± 1.17        |
| Tinnitus                            | 2.76 ± 1.33        |
| Sinus congestion                    | 2.60 ± 1.28        |
| Hearing loss                        | 2.22 ± 1.30        |
| Sensory 2                           |                    |
| Temperature sensitivity             | 2.92 ± 1.06        |
| Dizziness                           | 2.57 ± 1.06        |
| Response to chemicals               | 2.69 ± 1.16        |
| Night sweats                        | 2.29 ± 1.26        |
| Abdominal                           |                    |
| Abdominal pain                      | 2.49 ± 1.23        |
| Diarrhea                            | 2.55 ± 1.22        |
| Nausea                              | 2.40 ± 1.20        |
| Respiratory                         |                    |
| Dyspnea                             | 2.32 ± 1.23        |
| Persistent cough                    | 1.97 ± 1.32        |
| Sore throat                         | 1.76 ± 1.26        |
| Swollen lymph                       | 1.53 ± 1.34        |
| Wheezing                            | 1.85 ± 1.27        |
| Epithelial                          |                    |
| Problems with teeth or gums         | 2.39 ± 1.46        |
| Rash                                | 1.90 ± 1.32        |
| Mouth sores                         | 1.04 ± 1.13        |
| Hair loss                           | 1.19 ± 1.36        |
| Burning after sex                   | 1.12 ± 1.44        |
| Other/mood                          |                    |
| Irritable                           | 3.02 ± 0.96        |
| Depressed                           | 2.85 ± 1.17        |

Veterans graded the severity of the 37 Kansas criteria symptoms as 0 = none, 1 = trivial, 2 = mild, 3 = moderate, or 4 = severe over the past 6 months. Calculated symptom score averages characterize the most debilitating and persistent symptoms for this group of veterans.

Additional Measures

49.5% met the GAD-7 criteria for moderate to severe anxiety with scores greater than 14.12 88.7% met the CFS criteria for CFS with fatigue with scores 3 or 4, at least 4 ancillary symptoms with scores >1, and the sum of scores for the eight ancillary symptoms greater than or equal to 14.13 PTSD was self-reported by 65.6%. Diagnosis was made in 18.5% of veterans before 2000, 32.0% between 2000 and 2009, and 49.5% since 2010, indicating a delayed onset of PTSD symptomatology.

Over the previous week, 91.8% of veterans reported having taken pain medication, including narcotics or over-the-counter medications, at least once. 39.6% reported taking pain medication one or two times daily and 37.9% reported three or more times daily. 7.8% reported having been hospitalized for substance abuse or a psychiatric disorder. 70.7% reported symptoms worsening when walking a long distance suggesting the presence of post-exertional malaise. 60.8% reported having been told their condition “is all in their head.”

DISCUSSION

This sample of veterans with GWI created a valuable dataset of historical medical information and illustrated the current experience of this afflicted population by responding to an online questionnaire. The feasibility of using social media to access Gulf War veterans was demonstrated by this study, and the outcomes can be used to power larger and more targeted investigations in the future. The questionnaire may be of value for clinical research studies to approximate symptom severities across subjects, as a component of Common Data Elements, or for use in medical clinic examinations.

Symptom severity for the past 6 months demonstrated a high current burden of disease for veterans. While it is important to acknowledge that all respondents, by definition, suffer from moderate-to-severe symptoms, more than 89% of veterans reported having experienced every measured fatigue, pain, and abdominal symptom within the past 6 months. An overwhelming majority of veterans reported moderate or severe fatigue/sleep (84–91%) and pain (81–89%) symptoms over this time period as well. Most reported moderate-to-severe cognitive dysfunction with difficulty concentrating (80%) and problems remembering recent information (80%). While this study does not compare symptoms over the past 6 months to an age-matched nondeployed veteran group, it is apparent that the percentage of Gulf War veterans experiencing moderate-to-severe symptoms most likely exceeds the expected norm for Gulf War era veterans.

The degree to which veterans reported unusual sensory symptoms further emphasizes the unique experience of this population. Numbness and tingling in extremities (72%), low tolerance for heat or cold (69%), photosensitivity (62%), and self or partner having a burning sensation after sex (24%) may indicate dysfunctional somatosensory and interoceptive sensing systems.16,17 The reorganization of the symptoms...
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FIGURE 1. Gulf War illness symptom severity scores for the past 6 months grouped according to observed trends. Veterans graded the severity of the 37 Kansas criteria symptoms as 0 = none, 1 = trivial, 2 = mild, 3 = moderate, or 4 = severe. Percentages of the population reporting each level of severity are plotted and patterns can be seen among the symptom groups.

FIGURE 1 (continued). Gulf War illness symptom severity scores for the past 6 months grouped according to observed trends. Veterans graded the severity of the 37 Kansas criteria symptoms as 0 = none, 1 = trivial, 2 = mild, 3 = moderate, or 4 = severe. Percentages of the population reporting each level of severity are plotted and patterns can be seen among the symptom groups.

Latent symptom development is an additional component of GWI that encourages future investigation. The veterans who participated in this study reported cumulative frequencies higher than the point prevalence in a meta-analysis of 21 GWI large epidemiologic cross-sectional studies for symptoms around 1998.11 It is important to note that neither incidence nor prevalence can be estimated from the veterans’ retrospective recall of symptom onset. Cumulative frequency would overestimate prevalence if a symptom was experienced by a veteran at some point in their disease course but then subsided; it is expected that many of these symptoms would wax and wane over time. Although incidence cannot therefore be calculated, the positive slope of the cumulative frequency

of Serving in the Gulf War; “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.”2 This study supports this claim while also demonstrating a high level of comorbid mental illness in this population. While it continues to prove difficult to unveil the etiology and pathophysiology of GWI so many years post-deployment, this study highlights the need for better understanding the GWI experience today, including perceived barriers to care, types of treatment sought, and types of treatment received.

Additionally, the fact that 60.8% of veterans reported having been told their condition “is all in their head” calls into question other challenges faced by this unique population when seeking care. This question was investigated based on the Institute of Medicine’s 2016 Update on Health Effects
FIGURE 2. Gulf War illness symptom onset cumulative frequencies compared to moderate or severe symptoms for the past 6 months and previously published meta-analysis point prevalence data. Cumulative frequencies of symptoms, grouped according to visually identified symptom patterns, are plotted over time. Meta-analysis data for point prevalence of symptoms published in at least three studies are plotted for comparison. Filled shapes represent the prevalence for deployed personnel and open represent nondeployed personnel. The 95% confidence intervals are displayed for the meta-analysis data. The percentage of veterans reporting moderate or severe symptoms in the past 6 months are plotted as well, comparing current cumulative frequencies and present burden of disease.

indicates that new cases of symptoms have developed over the years. This supports that latent symptom development is a component of GWI and ongoing surveillance of impacted veterans is essential to give them appropriate care and to continue to monitor the health effects of hazardous war exposures. Future studies will be needed to distinguish between GWI and symptoms related to cardiovascular disease, diabetes, degenerative arthritis, cognitive decline, and other aspects of aging.

The major limitation of this study is recall bias, requiring veterans to self-report all health and military service information without a confirmatory history and physical exam or recourse of military or VA medical system records. However, approximating dates of onset may lead veterans to report symptoms as common themes. This may be useful for clustering symptoms together by pathophysiological mechanisms in future studies. Often, a patient’s historical recollection often is the only publicly available source of information about the patterns and timing of symptom onset. Data documenting symptom onset in the 1990s was not adequately recorded, so the veterans’ memory and personal documents are the only complete sources of historical information. The survey design attempted to minimize recall bias by grouping years of onset to include in theatre, shortly after the Gulf War from 1992 to 1994, and then 5-year increments following. It would be challenging for veterans to identify an exact onset year unless they were able to associate the start of a specific symptom with a single event.

Ascertainment bias may also exist due to recruitment via social media groups for Gulf War veterans; these veterans may possess a greater awareness of Gulf War-related health
problems and increased motivation to report their symptoms. Participants may have been more likely to participate if they experience more moderate-to-severe symptoms. Veterans simply unmotivated to respond were not sampled in this study but would also be unlikely to reply to postal surveys or recruitment to clinical research projects. Veterans who developed symptoms that subsequently resolved were not included, so these study data only apply to those who had long-term chronic problems. These issues can be addressed by future studies that include representative samples of deployed and nondeployed Gulf War era veterans.

While further studies are needed to uncover etiologic and pathophysiologic underpinnings of GWI, the dataset from this study has highlighted the current burden of disease for this veteran population and revealed symptom onset patterns that can be used as historical data for future military deployment research. For example, symptom clusters could be compared to other veteran groups such as those deployed in Operation Iraqi Freedom and Operation Enduring Freedom, those who have suffered traumatic brain injury, or any combat veteran having experienced hazardous war exposures post 9/11 to provide new epidemiologic insights. Destigmatization of GWI through understanding the severity and assortment of symptoms and their causes may prevent future cohorts of veterans who develop unexplained medical illness from war exposures from being told it is “all in their heads.”

CONCLUSIONS

GWI continues to be the predominant health concern of veterans deployed in the Persian Gulf region in 1990 to 1991. Ongoing studies are searching for answers regarding the etiology and pathophysiology of GWI. This study provides more long-term epidemiological data regarding disease course and current symptoms. The cumulative symptom frequencies in this study are higher than cross-sectional studies previously published and severity scores over the past 6 months demonstrate a high burden of disease. The results of this study can contribute to the ongoing surveillance of Gulf War veterans and inform the future medical care of other combat veterans experiencing health effects from exposures of war.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at MILMED online.

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