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Method Issues in Epidemiological Studies of Medically Unexplained Symptom-based Conditions in Veterans

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Abstract

Symptom-based conditions such as chronic fatigue syndrome (CFS) and medically unexplained multi-symptom illness (MSI) are fairly common in the general population and are also important veteran's health concerns due to their higher frequency among U.S. veterans who served during the 1990–1991 Gulf War. CFS, MSI, and other symptom-based conditions are often associated with considerable morbidity due to fatigue, chronic pain, neurologic symptoms, and other symptoms that can impair the quality of life. This article discusses several important issues of methodology that arise in population studies of CFS and MSI. These include the exclusion criteria that have been used in population studies to define CFS-like illness and unexplained MSI, the potential for false positive and false negative assessments of illness status, the potential for sex differences, and the poorly understood natural history of these symptom-based conditions across the life span. As an empirical example of these methodology issues, we examined existing data from a 2005 follow-up survey. We found that 64.9% (762 of 1,175) of female Gulf War veterans and 53.4% (2,530 of 4,739) of male Gulf War veterans had 1 or more exclusionary medical conditions. The prevalence among veterans with one or more exclusionary medical conditions increased markedly by age among females and those with a low income.

Keywords

chronic fatigue syndrome; medically explained multi-symptom illness; epidemiologic methods; menopause; Gulf War; survey; veterans

Symptom-based conditions are commonly seen in medical, neurologic, and psychiatric practice and are frequently the focus of epidemiologic studies, including those conducted to monitor the health and well-being of military and veteran populations. There has been extended discussion in the epidemiologic literature on how best to assess symptom-based conditions that are well-recognised in medicine and psychiatry—and for which diagnostic tests, procedures, or other clinical assessments are available—including those that are idiopathic or for which the causal mechanisms are only partly understood. Symptom-based conditions that are the focus of acute outbreak investigations have also been discussed in the

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literature on field epidemiology and emergency response. However, much less attention has been given to the epidemiologic assessment of health conditions that have no universally accepted medical diagnosis and cannot be further characterised by laboratory or diagnostic tests, particularly assessments that are included in longitudinal studies conducted over long periods of time.

We identified several important methodologic issues that arise in epidemiological studies of medically unexplained multi-symptom illness (MSI) in the course of planning two related national surveys of U.S. veterans (a follow-up survey of an established panel of veterans and a new survey and biorepository initiative), which are part of the Department of Veterans Affairs (VHA) coordinated efforts to carefully monitor the health and well-being of veterans who served during the 1990–1991 Gulf War.

Background

Results from epidemiologic studies indicate that U.S.-veterans who served in the 1990–1991 Gulf War are more likely to have medically unexplained multisymptom illness (MSI) than veterans who served during the same era but were not deployed to the Gulf[1,2]. Symptom-based conditions such as unexplained MSI and chronic fatigue syndrome-like (CFS-like) illness are health conditions of exclusion in that established medical diagnoses that may account for fatigue, chronic pain, or other debilitating symptoms first have to be excluded in order to identify possible cases. Psychiatric illnesses such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) are an exception to this rule; they can co-occur with unexplained MSI and CFS-like illnesses even though MDD and PTSD have been associated with chronic pain and fatigue. Epidemiologic studies have shown that deployment to the Gulf during the 1990–1991 war is associated with unexplained MSI and CFS-like illness even after adjustment for PTSD and MDD.[3,4]

Definitions of symptom-based conditions have varied across studies of Gulf War era veterans. For example, in the Longitudinal Health Study of Persian Gulf War Era Veterans[5], unexplained MSI was assessed using self-reported information about physical symptoms and illnesses (fatigue, muscle or joint pain, headaches, memory problems, digestive problems, respiratory problems, and skin problems) that persisted for 6 months or longer and were not adequately explained by an established, conventional medical or mental disorder diagnosis. Such unexplained physical symptoms and illnesses, which are often not labeled, are sometimes diagnosed as chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, or multiple chemical sensitivity. This study also used a modified version of the 1994 Centers for Disease Control and Prevention case definition of CFS[6] which takes into account differences in time frame[5]. CFS-like illness consisted of persistent problems in the past 12 months with fatigue lasting > 24 hours after exertion and persistent problems with at least three of seven symptoms (headaches, sore throat, tender lymph nodes, muscle aches or cramps, joint aches or pain, awakening feeling tired or worn out after a full night of sleep, and difficulty concentrating or reasoning or memory loss) and none of the following medical conditions: arthritis, skin cancer, other cancer, cirrhosis of the liver, hepatitis, diabetes, other endocrine disorder, repeated seizures or convulsions or blackouts, neuralgia or neuritis, disease of genital organs, coronary heart disease, stroke or cerebral vascular accident, tachycardia or rapid heart, asthma, emphysema or chronic bronchitis, and repeated bladder infections[5].

Another example of a modified definition was used in an epidemiologic study of illnesses among Gulf War veterans in Kansas[7]. They used a modified version of the CDC case definition of chronic MSI[8] that excluded veterans who had one or more medical conditions (cancer other than non-melanoma skin cancer, diabetes, heart disease other than high blood

pressure, chronic infectious disease, liver disease, lupus, multiple sclerosis, stroke, bipolar disorder, schizophrenia) or who had been hospitalised since the Gulf War for depression, post-traumatic stress disorder, or alcohol or drug dependence.[7] There are several other examples of diverse exclusion criteria used to assess symptom-based conditions in epidemiologic studies of veteran and non-veteran populations. In some studies of symptom-based conditions, physical exams and biomedical assessments have been performed.[8–10] Efforts have been made (and are continuing to be made) to arrive at consensus definitions of these conditions that are suitable for epidemiologic research, clinical trials, or medical practice.[6,11]

False Negative And False Positive Assessments Of Multi-Symptom Illness

It has now been over 20 years since the 1990–1991 Gulf War, and there is ongoing interest in re-contacting established panels of Gulf War and Gulf Era veterans to conduct additional follow-up surveys, enhance existing studies by establishing biological repositories, and facilitate translational clinical research aimed at providing effective, evidence-based treatment, including complementary and alternative medicine therapy. In order to assess the frequency of symptom-based conditions in repeat follow-up surveys, it is necessary to consider both false positive and false negative assessments of these conditions at two or more time points.

For example, comparisons of symptom-based conditions in surveys conducted in 2005 and 2012 would need to consider the possibility of misclassification of symptom-based conditions at one or both time points, as well as the comparability of exclusion criteria. It is conceivable that these symptom-based conditions may wax and wane over time, similar to autoimmune conditions such as multiple sclerosis. This natural variation could contribute to misclassifications in assessment of symptom-based conditions based upon self-reported data or clinical examinations conducted at any time point. Results obtained from such studies conducted a few years following the 1990–1991 Gulf War suggested a potential for misclassification or resolution of self-reported symptoms[10,12]. It is possible that these symptom-based conditions may go into remission, resolve entirely, or, conversely, worsen over time. There is also very little known about the possible impact of treatment for PTSD, alcohol dependence, or other deployment-related health conditions on the course of symptom-based conditions.

Exclusion Criteria For Multi-Symptom Illness and Age

The use of exclusion criteria for medical illnesses in assessing symptom-based conditions is scientifically defensible given the fact that these health concerns are conditions of exclusion. However, almost half of men and women in the general U.S. population have one or more chronic illnesses (for example, diabetes, cardiovascular disease, rheumatoid arthritis, chronic obstructive pulmonary disease, or neurodegenerative illness) and the percentage rises steeply with advancing age.[13,14] There has been little or no discussion in the literature about the impact of chronic illness or co-morbid chronic illnesses on the assessment of the population burden of symptom-based conditions in aging cohorts of veteran or non-veteran populations.

A further issue is that the population prevalence of some age-related chronic health conditions that can be associated with fatigue or chronic pain, such as obesity and osteoporosis-related fractures, have not traditionally been included as exclusion criteria for symptom-based conditions. Several authors have noted the high and increasing prevalence of overweight and obesity in veteran populations and in the general U.S. population.[15–17] We are unaware of any published information about whether the development of obesity worsens symptom-based conditions among 1990–1991 Gulf War era veterans. However, there have been studies of morbid obesity and metabolic syndrome among women in the

general population who suffer from CFS.[18–19] Obesity, which is an established risk factor for several chronic diseases including coronary heart disease, diabetes, arthritis, and some forms of cancer, is associated with higher levels of inflammatory markers such as interleukin-6 and tumour necrosis factor-alpha.[20]

Multi-Symptom Illness And Gender

The published literature on the health of U.S. veterans indicates that symptom-based conditions are more common among men and women who had been deployed to the Gulf during the 1990–1991 conflict, as compared with men and women who had served during the same era but who had not been deployed to the Gulf.[1,2,5,21] Sex-differences have also been noted, with women at higher odds of reporting symptom-based conditions than men.[22] We are unaware of any published information about the relative impact of exclusion criteria for medically unexplained symptom-based conditions in women versus men, including those who served in the 1990–1991 Gulf War. However, because women veterans who served during the 1990–1991 Gulf War era are only now approaching the age at which they may be peri-menopausal or post-menopausal, the possible impact of menopausal status on symptom-based conditions in veteran populations is unknown. This is an important gap in our current understanding of the natural history of medically unexplained symptom-based conditions, particularly since some scientific theories about the causation of CFS and unexplained MSI focus on neuro-immune mechanisms.

Menopause has effects on a number of organ systems including the cardiovascular, skeletal, central nervous, and genitourinary systems.[23] Clinical research studies have shown that women who are peri-menopausal and post-menopausal also undergo important changes in immune function.[24] Early menopause is a risk factor for rheumatoid arthritis, and post-menopausal status is associated with greater tissue damage and disability in rheumatoid arthritis.[23] Studies have shown that following menopause, women can experience an increase in pro-inflammatory serum markers such as interleukin-1, interleukin-6, and tissue necrosis factor-alpha.[24] In non-veteran populations, there has been very little research on menopausal status and CFS. A recent case-control study of gynaecological history and CFS among civilian women in Wichita, Kansas found that a greater proportion of women with CFS than controls reported pelvic pain unrelated to menstruation (22.2% vs. 1.7%, p=.004), and periods of amenorrhea (53.9% vs. 46.2%, p=.06) (24). Menopause occurred about 4.4 years earlier in the CFS group (41.7 years vs. 46.1 years, respectively, p=.11), even though the mean ages of the cases and controls were very similar.[25]

Empirical Example

In order to illustrate these issues, we examined existing data from a 2005 follow-up health survey among population-based samples of 15,000 Gulf War Veterans and 15,000 Gulf Era Veterans who served in the military during the same era but who were not deployed to the Persian Gulf.[5] Our goal was to obtain the frequency of exclusionary medical conditions in these samples according to broad age categories in order to estimate what the overall frequency of excludeable medical conditions might be as the cohort of veterans ages. This analysis does not take into account possible cohort effects that might occur due to temporal changes in the prevalence of chronic disease risk factors, but it does provide useful information for study planning purposes and for thoughts on methodology issues.

Study population—The sampling frame consisted of 15,000 Gulf War Veterans and 15,000 Gulf Era Veterans selected for an earlier 1995 survey. Kang et al.[26] sampled Gulf War Veterans from 693,826 U.S. troops who were identified by the Department of Defense Manpower Data Center in Monterey, California as being deployed to the Persian Gulf area during the 1991 Gulf War. They sampled Gulf Era Veterans from 800,680 persons who

represented about one half of all troops who were in the military between September 1990 and May 1991 but who did not serve in the Persian Gulf theatres of operations.

Branch of service (Army, Navy, Air Force, and Marine Corps) and unit component (active, reserve, and National Guard) were represented in both groups. Kang et al.[26] applied a stratified random sampling method to ensure that women and those who served in the reserve or National Guard were adequately represented. Approximately 20% of the sample were women. The survey data collection methods followed a modified Dillman method[27]; additional details may be found in previous publications.[5] About 26.8% of the Gulf War and Gulf Era Veterans in this sample (n=9,970) had unexplained MSI; the percentage with MSI was higher among those who had been deployed.[5] About 7.1% of the Gulf War and Gulf Era Veterans in this sample had a CFS-like illness; the percentage with CFS-like illness was higher among those who had been deployed.[5]

Current analysis—For our empirical example, we used the same criteria for CFS-like illness that were used in previous analyses of these data[4,5] except that we did not exclude those who reported they had ever been told by a doctor that they had skin cancer (since most cases of skin cancer in this population would not be melanoma). As noted above, these criteria consisted of a modified version of the 1994 Centers for Disease Control and Prevention case definition of CFS illness[6] which takes into account differences in time frame.[5] We also used the criteria for unexplained MSI that were used in published articles from the Longitudinal Health Study of Persian Gulf War Era Veterans.[5] Explanatory information in the survey questionnaire informed respondents that: “The following questions ask about unexplained multisymptom illnesses, that is having several different symptoms together that persist for 6 months or longer and are not adequately explained by conventional medical or psychiatric diagnoses…” Respondents were asked: “Since January 1991, have you ever experienced unexplained multisymptom illness that lasted 6 months or longer?” Thus, it was possible for respondents to self-report that they had unexplained MSI and to also report (earlier in the questionnaire) that they had been told by a doctor that they had 1 or more medical conditions considered to be exclusionary in other case definitions.[6]

Variables used in this example—The variables used included age in 2005 (categorized as <40, 40 to 49, 50 to 59, 60+ years), education (<high school, high school or equivalent, some college, associate degree, bachelor’s degree, or graduate degree), income (<$20,000, $20,000–34,999, $35,000–49,999, $50,000–74,999, $75,000–99,999, >$100,000), deployment status (Gulf War, Gulf Era), and unexplained MSI (yes/no). We created a dichotomous variable coded as ‘1’ if the respondent reported being told by a doctor that they had 1 or more of the exclusionary medical conditions, and ‘0’ otherwise. Using SAS, we performed cross-tabulations of these variables as well as a logistic regression analysis in which the dependent variable indicated whether or not the respondent reported being told by a doctor that they had 1 or more of the exclusionary medical conditions (1=yes, 0=no).

Results—The demographic and military characteristics of this sample have previously been detailed[4,5,15] The mean ages of the Gulf War (n = 6,111) and Gulf Era (n = 3,859) veterans who participated in 2004–2005 were 45.5 and 47.6 years, respectively. About 20.1 and 21.8 percent of respondents were women.

We found that the crude prevalence of unexplained MSI was 36.2% and 11.6% in the deployed and nondeployed groups, respectively, with a crude odds ratio of 4.33 (95% CI 3.87, 4.86), and an odds ratio of 4.25 (95% CI 3.78, 4.79) when adjusted for sex, education, and income. When persons who self-reported that they had been told by a doctor that they had 1 or more exclusionary medical conditions were considered not to have unexplained MSI, the crude prevalence of unexplained MSI was 9.7% and 2.6% in the deployed

(n=5,788) and nondeployed groups (n=3,714), respectively. However, the crude odds ratio of unexplained MSI comparing deployed to non-deployed increased to 5.08 (95% CI 4.05, 6.38) and 4.76 (95% CI 3.78, 6.00) when adjusted for sex, education, and income. In other words, when persons with a medical history of 1 or more of the exclusionary medical conditions are considered not to have unexplained MSI (but are retained in the denominator), the observed prevalence of MSI decreases considerably but the crude odds ratio of MSI (comparing deployed and non-deployed groups) increases. This is consistent with increased specificity of the case definition and a corresponding decrease in misclassification.

About 64.9% (762 of 1,175) of female Gulf War veterans and 53.4% (2,530 of 4,739) of male Gulf War veterans had 1 or more exclusionary medical conditions. Among male Gulf War veterans, the percentage with 1 or more exclusionary medical conditions increased markedly by age category (<40, 40 to 49, 50 to 59, 60+ years): 41.8%, 50.9%, 65.5%, and 73.1%, respectively. Among female Gulf War veterans, the percentage with 1 or more exclusionary medical conditions also increased by age category (<40, 40 to 49, 50 to 59, 60+ years): 56.4.8%, 63.4%, 78.8%, and 89.6%, respectively. Non-linear relationships were observed between educational attainment and the percentage with 1 or more exclusionary medical conditions in both male and female Gulf War veterans. About 65.2% of Gulf War veterans with less than a high school education had one or more exclusionary medical conditions compared with 55.6% of those with a high school education, college degree, or graduate degree. Income was strongly associated with the percentage with 1 or more exclusionary medical conditions, except among the relatively small number of women who were 60+ years of age. Among male Gulf War veterans with a reported income of <$20,000, 72.8% (386 of 530) had 1 or more exclusionary medical conditions compared with 49.5% (358 of 723) of those with an income of >$100,000 per year.

The overall pattern was similar for Gulf Era veterans, except that the frequency with 1 or more exclusionary medical conditions tended to be lower than in the Gulf War veterans. About 61.9% (508 of 821) female Gulf Era veterans and 47.7% (1,393 of 2,923) of male Gulf Era veterans had 1 or more exclusionary medical conditions.

In multivariate analysis using logistic regression (Table 1), advancing age, female gender, and deployment status were positively associated with having 1 or more exclusionary medical conditions (p<.001 in each instance). Annual household income was strongly and inversely associated with having 1 or more exclusionary medical conditions (p<.0001).

Discussion

To our knowledge, no epidemiological studies have examined CFS-like illness and unexplained MSI over 2 or more decades of life among U.S. veterans or members of the general population, although the VHA has efforts underway to address this important gap in scientific knowledge. A recent report by Li et al.[28] examined changes in health status in U.S. veterans who served during the 1990–1991 Gulf War era over a 10-year period (1995–2005). At 10-year follow-up, deployed veterans were more likely to report persistent poor health, repeated clinic visits, recurrent hospitalisations, CFS-like illness, and PTSD, than non-deployed veterans. In addition, deployed veterans were more likely to experience new onset of adverse health and certain chronic diseases than were non-deployed veterans, after adjustment for age and other confounding factors.[28]

As highlighted in our report, criteria for medically unexplained symptom-based conditions such as CFS and CFS-like illness require that persons with a history of certain medical conditions (e.g., cancer, heart disease, diabetes) be excluded. This is an important

consideration in longitudinal studies of the natural history of CFS and unexplained MSI in both veteran populations and samples of the general U.S. population, particularly since the prevalence of chronic conditions such as diabetes and obesity have increased in recent years and both men and women are at increased risk of several chronic medical and neurodegenerative conditions as they get older.[15,16] A very high percentage of older men and women who participated in the 2005 survey,[5] particularly the older women, self-reported being told by a doctor that they had 1 or more of the exclusionary medical conditions, and thus would not be considered to have unexplained MSI or CFS according to "strict" criteria such as those used by Steele et al.[7] in their study in Kansas. It is also important to note that "strict" criteria for unexplained MSI exclude a very high percentage of U.S. veterans who served in the 1990–1991 Gulf War or during the same era who had low income or less educational attainment. This may contribute to a perception that unexplained MSI is a condition of the relatively affluent and well-educated. Policy decisions about optimal case definitions for symptom-based conditions should take into account both scientific considerations (e.g., approaches for increasing specificity and decreasing misclassification) and the potential impact on vulnerable groups of veterans.

Although our empirical example uses data from a cross-sectional survey conducted in 2005 to project the age-specific frequency of exclusionary medical conditions in the future, our estimates are likely to be conservative because:

1. we did not take into account a self-reported history of alcohol dependence, serious psychiatric illness, or HIV/AIDS, and
2. the population frequencies of obesity, diabetes, and certain other chronic medical conditions which have increased in the U.S. over the past several years.

Nonetheless, these data provide a quantitative assessment of how definitions and exclusion criteria for symptom-based conditions can potentially introduce statistical bias, especially in an ageing population. Continued discussion and empirical analyses are likely to contribute to new or updated consensus definitions of symptom-based conditions that are suitable for longitudinal epidemiologic research.

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Table 1

Adjusted odds ratios from logistic regression modeling of having 1 or more exclusionary medical conditions.

Covariate	Adjusted odds ratio (95% CI)
Age in 2005 (years)**	
<40	1.00*
40 to 49	1.47 (1.32–1.63)
50 to 59	2.86 (2.55–3.22)
60 +	4.31 (3.62–5.12)
Sex**	
Male	1.00*
Female	1.93 (1.73–2.15)
Deployment status**	
Gulf Era	1.00*
Gulf War	1.32 (1.21–1.44)
Education**	
< High school	1.00*
High school degree	1.05 (0.68–1.61)
Some college, no degree	1.26 (0.82–1.92)
Associate degree	1.13 (0.73–1.75)
Bachelors degree	0.96 (0.60–1.43)
Masters, doctorate, or professional degree	1.11 (0.71–1.72)
Annual household income**	
<$20,000	1.00*
$20,000 to $34,999	0.59 (0.49–0.72)
$35,000 to $49,999	0.48 (0.40–0.58)
$50,000 to $74,999	0.42 (0.35–0.50)
$75,000 to $99,999	0.39 (0.32–0.48)
>$100,000	0.36 (0.29–0.44)

* Referent category.

** p<.0001 from Wald chi-square test.