Is Systemic Lupus Erythematosus, Amyotrophic Lateral Sclerosis, or Fibromyalgia Associated with Persian Gulf War Service? An Examination of Department of Defense Hospitalization Data

Tyler C. Smith, Gregory C. Gray, and James D. Knoke

Since the Persian Gulf War ended in 1991, veterans have reported diverse, unexplained symptoms. Some have wondered if their development of systemic lupus erythematosus, amyotrophic lateral sclerosis, or fibromyalgia might be related to Gulf War service. The authors used Cox proportional hazard modeling to determine whether regular, active-duty service personnel deployed to the Persian Gulf War (n = 551,841) were at increased risk of postwar hospitalization with the three conditions compared with nondeployed Gulf War era service personnel (n = 1,478,704). All hospitalizations in Department of Defense facilities from October 1, 1988, through July 31, 1997, were examined. With removal of personnel diagnosed with any of the three diseases before August 1, 1991, and adjustment for multiple covariates, Gulf War veterans were not at increased risk of postwar hospitalization due to systemic lupus erythematosus (risk ratio (RR) = 0.94, 95% confidence interval (CI): 0.65, 1.35). Because of the small number of cases and wide confidence limits, the data regarding amyotrophic lateral sclerosis were inconclusive. Gulf War veterans were slightly at risk of postwar hospitalization for fibromyalgia (RR = 1.23, 95% CI: 1.05, 1.43); however, this risk difference was probably due to the Gulf War veteran clinical evaluation program beginning in 1994. These data do not support Gulf War service and disease associations.

The possibility of associations between Persian Gulf War-related exposures and unusual postwar illnesses has received considerable attention in both the popular media and the medical literature (1–5). Since returning from the war, many of the nearly 700,000 service personnel have reported a broad range of unexpected symptoms (6–8). Although the causes of these symptoms remain unknown, strategies have been developed to attempt to identify and define Gulf War-related illnesses. Recent epidemiologic studies have found no unusual increases in birth defects (9, 10), hospitalization (11, 12), or mortality (13, 14) among Persian Gulf War veterans when compared with nondeployed veterans of the same era. However, concerns have been expressed regarding the possibility of masking population risk differences for specific diagnoses when many diagnoses are grouped together.

We sought to examine the association of Gulf War service with three specific diseases that have gained attention from veterans’ groups, expert panels, and researchers (3, 15–20): 1) systemic lupus erythematosus (SLE), a chronic autoimmune disease that causes inflammation in various parts of the body, especially the skin, joints, blood, and kidneys; 2) amyotrophic lateral sclerosis (ALS), a motor neuron disease caused by the gradual degeneration of nerve cells in the brain and spinal cord; and 3) fibromyalgia, a chronic condition characterized by generalized aches, pains, and stiffness in muscles and tendons.

MATERIALS AND METHODS

Population

The study population consisted of all regular active-duty military personnel who were either deployed to the Persian Gulf War theater for one or more days during the Gulf War deployment period, August 8, 1990, through July 31, 1991, or who were not deployed but...
were on active duty for at least part of the deployment period (11).

The study focused on regular active-duty personnel because their military hospitalization data are available electronically and they are seldom hospitalized outside of Department of Defense facilities (11, 21). Members of the US Reserve and National Guard forces are generally not hospitalized in military facilities and therefore were not included in this investigation.

Deployment and demographic data were provided by the Defense Manpower Data Center, Seaside, California. Gulf War veteran demographic data included age, sex, marital status, race (White, Black, Hispanic, and "other"), service branch (Army, Navy, Marine Corps, Air Force, and Coast Guard), service type (active duty, National Guard, and US Reserve), rank (enlisted, warrant officer, and commissioned officer), Persian Gulf War deployment status, and number of days in the Persian Gulf arena (categorized by approximate quartiles to 1–92 days, 93–149 days, 150–197 days, 198–572 days). These demographic variables, evaluated at the time of the Gulf War, were studied for possible associations with SLE, ALS, and fibromyalgia.

Hospitalization data

Hospitalization data were captured from all Department of Defense hospitals from October 1, 1988, through July 31, 1997, and included the date of admission and up to eight individual discharge diagnoses. Diagnoses were coded according to the International Classification of Diseases, Ninth Revision (ICD-9) (22). All hospital admissions with an ICD-9 code for SLE (710.0), ALS (335.20), or fibromyalgia (729.1) were extracted. Hospitalization data for the period of October 1, 1988, through July 31, 1991, were scanned for one or more of these diagnoses. If a diagnosis was found, the subject was removed from further analyses. Additionally, as in previous reports (11, 23, 24), a prewar hospitalization covariate was created to denote an individual's hospitalization for any cause during the 12 months prior to August 1, 1990.

Comprehensive Clinical Evaluation Program data

The Department of Defense Comprehensive Clinical Evaluation Program (CCEP) is a voluntary registry for active duty service members to evaluate, document, diagnose, and treat conditions that may have arisen subsequent to service in the Persian Gulf War arena (8, 25, 26). It was instituted in June 1994 to serve Gulf War veterans who have remained on active duty, retired from service, or who are currently serving in the National Guard or the US Reserves. The program consisted of a structured evaluation protocol, encompassing a comprehensive history and physical examination. If necessary, veterans were referred to specialists or referral hospitals for more advanced diagnostic tests and treatment. Clinical diagnoses, symptoms, and self-reported exposures were recorded for each participant. Active duty veterans were indicated as being participants in the CCEP registry by match merging CCEP participants with the study population.

Statistical analysis

Cox proportional hazard survival analysis modeling was used to compare the hospitalization experience of the Gulf War and nondeployed veterans. Subjects were classified as having an event if they were hospitalized in any Department of Defense hospital worldwide with a diagnosis of SLE, ALS, or fibromyalgia and as censored otherwise. Follow-up time was calculated from August 1, 1991, until hospitalization, separation from service, or July 31, 1997, whichever occurred first. An exploratory model analysis was first performed to assess the significance of the demographic covariates on the risk of the three diseases. Separate univariate analyses for the three outcomes yielded consistent sets of demographic covariates with \( p \) values of 0.10 or below, which were included in all subsequent model analyses.

The risk ratio and 95 percent confidence interval for deployment status and the demographic covariates were computed for the Cox models. Data management and statistical calculations were performed using the Statistical Analysis System (SAS Institute, Inc., Cary, North Carolina) (27).

RESULTS

All Gulf War \((n = 551,841)\) and nondeployed \((n = 1,478,704)\) veterans who had complete covariate data, did not have a diagnosis with any of the three diseases during the period of October 1, 1988, through July 31, 1991, and remained on active duty at the end of the deployment period were included in the study population. The average length of service after July 31, 1991, was 3.4 years (standard deviation, 2.3; range, 0.04–6.0) for Gulf War veterans and 3.8 years (standard deviation, 2.2; range, 0.07–6.0) for nondeployed veterans.

Systemic lupus erythematosus

During the period of October 1, 1988, through July 31, 1991, 12 Gulf War veterans and 38 nondeployed
veterans were hospitalized with a diagnosis of SLE. After these 50 personnel were removed from subsequent analyses, 36 Gulf War veterans and 160 nondeployed veterans were found to be hospitalized with SLE during the 6 years of postwar study. Women had more than 12 times the risk of men (table 1). The categories of Hispanic and "other" were not appreciably different from Whites; therefore, these three categories were combined and classified as non-Blacks. Blacks were at more than three times the risk of non-Blacks (table 1).

Increasing age was strongly associated with risk for SLE hospitalization (table 1). Other demographic covariates—branch of service, marital status, and being hospitalized prior to the start of the Gulf War—were not statistically significant and consequently were not included in final analyses. Rank was not included in the final analyses because of colinearity with age. Deployment status was not associated with SLE (risk ratio (RR) = 0.94, 95 percent confidence interval (CI): 0.65, 1.35).

Separate models for Gulf War veterans and nondeployed veterans were examined to determine if interaction was present between the demographic variables and deployment status; no appreciable interactions were apparent. Gulf War veterans were not at increased probability of hospitalization in comparison with nondeployed veterans during the 6 years of follow-up (figure 1).

**Amyotrophic lateral sclerosis**

During the period of October 1, 1988, through July 31, 1991, one Gulf War veteran and three nondeployed veterans were hospitalized with a diagnosis of ALS. These personnel were removed from postwar modeling. Because of the small number of subjects hospitalized after the war with ALS (six Gulf War veterans, 12 nondeployed veterans), not all demographic covariates were included in a single model analysis with deployment status. Separate model analyses were run for the different demographic covariates to determine which ones were significant influences on the risk of ALS and which categories of different covariates could be combined. The result was a manageable covariate load on the model with age and deployment status as covariates. Branch of service, marital status, race, sex, and prewar hospitalization were not statistically significant in the screening analyses and consequently were not included in the final models. Rank was also removed from the final models because of colinearity with age. Increasing age was strongly associated with hospitalization risk. Deployment status was not significantly associated with ALS (RR = 1.66, 95 percent CI: 0.62, 4.44).

Separate models for Gulf War veterans and nondeployed veterans were examined to determine if interaction was present between age and deployment status; no appreciable interaction was apparent. The two groups had the same probability of hospitalization for ALS during the first 3.5 years of follow-up, August 1991 to January 1995. After this time point there were no nondeployed cases to compare with the final two deployed cases.

---


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total no.</th>
<th>No. of cases</th>
<th>Adjusted RR*</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gulf War veteran</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not†</td>
<td>1,477,287</td>
<td>160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>550,153</td>
<td>36</td>
<td>0.94</td>
<td>0.65, 1.35</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male†</td>
<td>1,805,930</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>221,510</td>
<td>126</td>
<td>12.12</td>
<td>8.98, 16.36</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29 years</td>
<td>2,027,440</td>
<td>196</td>
<td>1.04</td>
<td>1.02, 1.07</td>
</tr>
<tr>
<td>30-39 years</td>
<td>1,610,997</td>
<td>85</td>
<td>3.61</td>
<td>2.71, 4.82</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Black†</td>
<td>418,443</td>
<td>111</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1,610,997</td>
<td>85</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* RR, risk ratio from Cox proportional hazards model; CI, confidence interval.
† Reference category.
Fibromyalgia

During the period of October 1, 1988, through July 31, 1991, 150 Gulf War veterans and 339 nondeployed veterans were hospitalized with a diagnosis of fibromyalgia. These personnel were removed from postwar modeling. During the 6 years of postwar study, 239 Gulf War veterans and 621 nondeployed veterans were hospitalized with fibromyalgia. Women had more than three times the risk of men (table 2). Increasing age was strongly associated with hospitalization risk. A person hospitalized prior to the start of the Gulf War had 1.6 times the risk of hospitalization with fibromyalgia. Army personnel had almost 3 times the risk of Navy personnel. Marines and Air Force personnel had approximately 1.5 times the risk of Navy personnel. The other demographic covariates—marital status and race—were not statistically significant and consequently were not included in the final models. Rank was not included in the final model analyses because of colinearity with age. Deployment status was found to be associated with hospitalization for fibromyalgia, with Gulf War veterans at 1.2 times the risk of hospitalization (RR = 1.23, 95 percent CI: 1.05, 1.43) compared with nondeployed veterans.

Separate models for Gulf War veterans and nondeployed veterans were examined to determine if interactions were present between the other covariates and deployment status. No appreciable interactions were detected. Gulf War and nondeployed veterans had the same probability of hospitalization for fibromyalgia during the first 3.5 years of follow-up (figure 2). At this point there was a noticeable increase for Gulf War veterans in the probability of being hospitalized. This increase in the probability was consistent with the inception of the Department of Defense CCEP in June 1994. To investigate this observation, we split the follow-up period into two time periods, before and after the inception of the CCEP. The model analysis of the time period before the inception of the CCEP, August 1, 1991, through June 30, 1994, showed no increased risk of hospitalization with fibromyalgia among Gulf War veterans (RR = 0.92, 95 percent CI: 0.74, 1.13). The model analysis of the time period after the inception of the CCEP, June 30, 1994, through July 31, 1997, showed almost twice the risk of fibromyalgia hospitalization among Gulf War veterans (RR = 1.76, 95 percent CI: 1.39, 2.22).

A CCEP participant covariate was created and added to the Cox model for the second time period to see if that variable would account for some of the variance in the model. The CCEP participants had more than 26 times the risk of being hospitalized with fibromyalgia than did nonparticipants (RR = 26.40, 95 percent CI: 18.62, 37.43). After the introduction of the CCEP covariate, Gulf War veterans’ risk markedly declined (RR = 0.56, 95 percent CI: 0.41, 0.78).


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total no.</th>
<th>No. of cases</th>
<th>Adjusted RR*</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gulf War veteran</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No†</td>
<td>1,478,186</td>
<td>621</td>
<td>1.23</td>
<td>1.05, 1.43</td>
</tr>
<tr>
<td>Yes</td>
<td>550,529</td>
<td>239</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prewar hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No†</td>
<td>1,886,083</td>
<td>745</td>
<td>1.63</td>
<td>1.33, 1.99</td>
</tr>
<tr>
<td>Yes</td>
<td>142,632</td>
<td>115</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male†</td>
<td>1,807,064</td>
<td>607</td>
<td>3.28</td>
<td>2.82, 3.82</td>
</tr>
<tr>
<td>Female</td>
<td>221,651</td>
<td>253</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>2,028,715</td>
<td>860</td>
<td>1.05</td>
<td>1.04, 1.06</td>
</tr>
<tr>
<td>Service</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Navy†</td>
<td>600,727</td>
<td>141</td>
<td>2.75</td>
<td>2.28, 3.33</td>
</tr>
<tr>
<td>Army</td>
<td>716,702</td>
<td>446</td>
<td>1.35</td>
<td>0.97, 1.89</td>
</tr>
<tr>
<td>Marines</td>
<td>196,643</td>
<td>47</td>
<td>1.35</td>
<td></td>
</tr>
<tr>
<td>Air Force</td>
<td>514,643</td>
<td>226</td>
<td>1.61</td>
<td>1.30, 1.98</td>
</tr>
</tbody>
</table>

* RR, risk ratio; CI, confidence interval.
† Reference category.
DISCUSSION

It has been suggested that Gulf War veterans may be suffering from SLE, ALS, and fibromyalgia due to war exposures. Recognizing data limitations, our analyses of the best available hospitalization data do not support such deployment-disease associations. Our risk factor findings were generally consistent with those in the published literature.

Systemic lupus erythematosus

Our finding that women were at increased risk for hospitalization with SLE is consistent with other reports that show women to have 10–15 times the risk of men (28). The finding that Blacks were at an increased risk over other races is also consistent with the literature (28, 29).

Amyotrophic lateral sclerosis

Our finding that older personnel were at a greater risk for acquiring ALS than were younger people is consistent with published literature (30, 31). Despite the very large number of study subjects, we detected sparse ALS outcomes, and our analyses are limited in statistical power to detect risk factor associations with ALS hospitalizations. This is evident by the broad confidence interval around the Gulf War veterans/nondeployed veterans’ adjusted postwar hospitalization risk ratio (RR = 1.66, 95% CI: 0.62, 4.44). Assuming similar conditions, we found these data to be only adequate to detect a statistically significant risk ratio of 2.82. Interestingly, a recent medical chart review by the Department of Veterans Affairs suggested that as many as 28 Gulf War veterans may have developed ALS after the war, suggesting an increased incidence compared with civilian populations (32). Further studies of ALS among Gulf War veterans are being planned.

Fibromyalgia

Much attention has been given to the diagnosis of fibromyalgia among Gulf War veterans (5, 17, 33, 34). Our finding of greater risk for females is consistent with the literature (35, 36). The finding that the Army and Air Force personnel were at a greater risk than were the Navy and Marine Corps personnel may have been a result of the increased CCEP hospitalizations by Army and Air Force hospitals. The effect of age on the outcome of fibromyalgia has not been previously reported and may be an artifact.

Our analyses showed a slightly increased risk of fibromyalgia hospitalization for Gulf War veterans versus nondeployed veterans. Six years after the conflict ended, the cumulative probability of hospitalization for fibromyalgia was 0.00048 percent for nondeployed veterans and 0.00061 percent for the Gulf War veterans (figure 2). This overall risk increase reflects a sharp temporal increase in risk beginning around June 1994. An analysis of the time period August 1, 1991, through June 30, 1994, showed no increase in risk for Gulf War veterans. The analysis for the time period June 30, 1994, through July 31, 1997, showed an almost twofold increase in risk for Gulf War veterans.

In June 1994, a strategy of admitting some CCEP participants at large Army and Air Force hospitals was adopted. This may have been responsible for causing an artificial increase in hospitalizations for fibromyalgia among Gulf War veterans. A recent report found a similar trend for diagnoses associated with hospitalizations due to unexplained illnesses (23). That report noted that several large Army and Air Force hospitals created special wards for the hospitalization of CCEP participants. These CCEP participants were admitted for extensive clinical evaluations, sometimes for several days. The admission of CCEP participants was discontinued in mid-1995, at which time the hospitalization curves for fibromyalgia again became nearly parallel (figure 2).

Adding a CCEP participant covariate to the analysis of the post-CCEP conception time period indicated that participation in the CCEP was a strong independent risk factor for fibromyalgia. CCEP participants had 26 times the risk of being hospitalized for fibromyalgia compared with nonparticipants. Our analysis suggests that the increase in hospitalizations for fibromyalgia among Gulf War veterans may be due to transient confounding by the strategy of hospitalizing CCEP participants for extensive evaluations during the first year the program was in existence.

Data limitations

These analyses have a number of limitations. A key limitation involves exposure classification. Gulf War exposure status was defined as those persons deployed to the Gulf War theater for one or more days during the deployment period. This broad classification does not account for specific exposures encountered during the deployment. Unfortunately, good quality data for specific Gulf War exposures are not available (3, 15, 16). We explored two surrogates for Gulf War exposure data: time in theater (days) and possible exposure to chemical munitions (three exposure categories) (37). Studying only Gulf War veterans, we individually examined these risk factors for associations with postwar hospitalizations with the three diseases (total of six models). Neither time in theater nor possible expo-
sure to chemical munitions was important in predicting the diseases (data not shown).

Our study is limited in ability to detect disease. Ideally, before we compared the two cohorts, we should have screened out all persons who had the diseases of interest prior to the war. We did so as best we could by examining all available hospitalization data back to October 1988. However, we recognize that we may have missed personnel who developed these diseases before that time or who were treated as outpatients. No electronic outpatient morbidity data are available until 1997. Additionally, our postwar hospitalization analyses would have detected only personnel who were ill enough to be admitted to hospitals. Our ascertainment of cases was further limited by departures from military service. Many personnel separated during the period of follow-up: 59.9 percent of the Gulf War veterans and 54.3 percent of the nondeployed veterans had separated by June 30, 1996. As no comprehensive national hospitalization databases are available (12), we could not identify individuals hospitalized in nonmilitary hospitals.

Study strengths

This study’s large population (n = 2,030,545) and the availability of important demographic covariates offer unusually high statistical power to detect differences between the two cohorts for SLE and fibromyalgia hospitalizations. We are confident that the available hospitalization data are nearly complete as active-duty personnel are seldom hospitalized outside of the Department of Defense system (11, 21).

Additionally, routine physical screening and frequent physical fitness testing of military personnel strengthen the probability of early detection of these diseases with subsequent hospitalization for evaluation, as compared with similar studies of civilian personnel not so screened. Finally, in preparation for separation from military service, personnel receive thorough medical screening and evaluations. They recognize the importance of reporting any symptoms or illnesses as they may receive lifelong disability benefits if a disorder or disease is found to be service connected. This causes them to be rather thorough in their reporting of symptoms and illness (21).

ACKNOWLEDGMENTS

This represents report no. 99-1, supported by the Department of Defense/Health Affairs, under NMRCDC reimbursable - 6423. A preliminary report of these data was presented at the Conference on Federally Sponsored Gulf War Veterans’ Illnesses Research in Pentagon City, Maryland, June 17–19, 1998. This study was conducted in accordance with Department of Defense and Department of the Navy instructions.

The authors thank Michael A. Dove and Wayne F. Woo from the Management Information Division, Defense Manpower Data Center, Seaside, California, for providing Gulf War veteran deployment data.

REFERENCES

19. Escalante A, Fischbach M. Musculoskeletal manifestations,


