Late Prevalence of Respiratory Symptoms and Pulmonary Function Abnormalities in Gulf War I Veterans

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Background: Published reports have documented an increased prevalence of self-reported respiratory symptoms among servicemen deployed during the 1990-1991 Gulf War. We evaluated whether this deployment resulted in long-term adverse respiratory effects.

Methods: A comprehensive medical history was taken and physical and laboratory evaluations, including pulmonary function tests, were performed in 1036 deployed and 1103 nondeployed veterans of the Gulf War. Participants were classified into 5 groups on the basis of their pulmonary function tests findings: normal pulmonary function; nonreversible airway obstruction; reversible airway obstruction; restrictive lung physiology; and small airway obstruction.

Results: Deployed veterans were younger, more commonly white, less educated, single, of lower mean family incomes, and more likely to have enlisted than nondeployed veterans. Deployed veterans were also statistically more likely to self-report a history of smoking and wheezing than nondeployed veterans, but comparisons of reported physician visits for pulmonary complaints, pulmonary hospitalizations, numbers of documented episodes of asthma, bronchitis, or emphysema, and pulmonary medications prescribed in the year prior to evaluation did not reveal any differences between deployed and nondeployed veterans. The distribution of pulmonary function test results was identical among deployed and nondeployed veterans. Among both deployed and nondeployed veterans, about 64% had normal pulmonary function, 16% to 18% had nonreversible airway obstruction, 10% to 12.2% had restrictive lung physiology, 6% to 6.7% had small airway obstruction, and the remaining 0.9% to 1.3% had reversible airway obstruction.

Conclusion: Our findings did not confirm the hypothesis that deployment to the Gulf War in 1990-1991 resulted in an increased prevalence of clinically significant pulmonary abnormalities 10 years later.

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BEGINNING IN AUGUST 1990, approximately 700,000 US military personnel, on active duty and from National Guard and Reserve units, were deployed to Saudi Arabia, Kuwait, Iraq, and other countries during Gulf War I. Military personnel were exposed to predeployment immunizations and to potentially harmful substances such as infectious and other biological agents, depleted uranium, oil well fire smoke, and chemical agents.

A variety of pulmonary symptoms have been reported by self-selected Gulf War American, British, and Canadian veterans, as well as more representative cohorts from Iowa, the northeastern United States, the US Air Force, and the United Kingdom. Phases I and II of a retrospective, population-based cohort study compared the self-reported health of 15,000 troops deployed to the Persian Gulf region from August 1990 to July 1991 with the health of 15,000 nondeployed troops and demonstrated that the prevalence of self-reported symptoms and illnesses related to the respiratory system was higher among deployed veterans (DVs).

To more objectively evaluate these findings, pulmonary histories (including symptoms and medication use) and objective measurements of pulmonary function were obtained as part of the National Health Survey of Gulf War Era Veterans and Their Families—a phase III survey initiated by the Department of Veterans Affairs Cooperative Studies Program. We examined whether Gulf War I deployment is associated with long-term detrimental pulmonary function effects.
STUDY POPULATION
The cohort for the present study (phase III) was derived from participants in phases I and II of the National Health Survey of Gulf War Era Veterans and Their Families. The survey included 69,382 veterans deployed to the theater of operations during Gulf War I and 80,680 nondeployed veterans, according to a stratified random sampling method detailed in a separate publication.\(^1\) This method produced a list of 20,917 veterans likely to live close to a research examination center. A final list of matched DVs and nondeployed veterans (NDVs) for whom address and telephone information was available was generated.

RECRUITMENT OF PARTICIPANTS
Participants were recruited from the 58,85 individuals on the list of matched DVs and NDVs. Examination sites were organized at 16 Veterans Affairs Medical Centers dispersed across the United States. Travel, hotel, per-diem costs, and an honorarium of $200 were provided to each participant and all gave informed consent. The project was approved by the Hines Cooperative Studies Coordinating Center and by the human rights committee and the institutional review board of each participating site.

DATA COLLECTION
Standardized comprehensive medical, psychiatric, neuropsychological, and laboratory examinations were performed between 1999 and 2001. All medications currently taken, whether prescribed or over the counter, were tabulated. In addition, pulmonary function tests (PFTs) were performed. Testing took 12 hours and was performed over 2 days.

Self-reported respiratory symptoms included cough, sputum production, and shortness of breath when climbing stairs. Participants who reported a history of (1) a physician visit for hospitalization for a respiratory problem, (2) inhaled corticosteroid use, and/or (3) bronchodilator use, either orally or via a corticosteroid metered-dose inhaler, were considered to be self-reporting a respiratory condition.

KHAMISIYAH EXPOSURE AND PFTS
In March, 1991, US demolition experts destroyed a munitions storage site at Khamisiyah, Iraq, possibly releasing the nerve agents sarin and cyclosarin. The risk of exposure was estimated by the Department of Defense by overlaying troop location data with meteorological and dispersion modeling.\(^13\) Approximately one seventh of all DVs were identified as having possibly been exposed.

In this study, PFTs were performed by the same credentialed and experienced technicians at each site. Participants using inhaled medications were told not to use them for 12 hours before testing. At least 3 forced expiratory maneuvers were performed by each participant before and after inhalation of 2 puffs of a standard bronchodilator. Participants were verbally encouraged to produce their best effort. The morphologic characteristics of the tracings were reviewed by the physician responsible for the pulmonary function laboratory as part of the laboratory’s quality control program at each site. Results of the best maneuver (highest absolute and percentage of predicted flow rates) were reported to the Hines Data Coordinating Center for analysis. Spirometers were standardized at each site but not across sites. Lung volumes and single-breath lung diffusion were not measured.

Participants were assigned to 1 of 5 categories based on their PFT results. Definitions of pulmonary functions were as follows:\(^14\)

- Normal pulmonary function (NPF): Prebronchodilator forced vital capacity (FVC) and prebronchodilator forced expiratory volume in 1 second (FEV\(_1\)) are both greater than 80% of predicted value, and the FEV\(_1)/FVC\) ratio is greater than 75% of predicted value.
- Nonreversible airway obstruction (NRAO): Prebronchodilator FEV\(_1)/FVC\) ratio is less than 75% of predicted value, with an improvement of 15% or less after bronchodilator use.
- Reversible airway obstruction (RAO): Prebronchodilator FEV\(_1\) and FVC are less than 80% of predicted value after correcting for body size, and FEV\(_1)/FVC\) ratios are less than 75% of predicted value; however, there is an improvement in FEV\(_1\) and/or FVC is greater than 15% after bronchodilator use.
- Restrictive lung physiology (RLP): Prebronchodilator FEV\(_1\) and FVC are less than 80% of predicted value after correcting for body size, but with normal FEV\(_1)/FVC\) ratios (>75% of predicted value). The percentages of predicted values for FEV\(_1\) and FVC were calculated using the prediction equations of Crapo et al.\(^15\) for men and women.
- Small Airway Obstruction (SAO): Prebronchodilator large airway function is normal (FEV\(_1)/FVC\) ratio > 75% of predicted value) but mid-maximal flow rates are reduced (maximal mid expiratory flow rate [MMEFR]\(25%-75%\) < 70% of predicted values). Predicted values for MMEFR\(25%-75%\) were calculated using the prediction equations of Crapo et al.\(^15\) for men and women as follows:

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\text{Men: Predicted Forced Expiratory Flow (FEF) }_{25%-75\%} = 0.0204 \times \text{Height in Centimeters} - (0.038) \times (\text{Age in Years}) + 2.133.
\]

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\text{Women: Predicted FEF }_{25%-75\%} = 0.0154 \times \text{Height in Centimeters} - (0.046) \times (\text{Age in Years}) + 2.683.
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DATA QUALITY ASSURANCE
A detailed operations manual, 3 prestudy comprehensive training meetings, and real-time twice-weekly conference calls with site staff provided instruction and resolved problems.\(^16\) All data were manually reviewed for accuracy and completeness by staff of the Hines Cooperative Studies Coordinating Center. Computer programs checked data for valid ranges and data consistency between data fields, and all data inconsistencies were corrected.

STATISTICAL ANALYSIS
The determination of target sample sizes of 1,000 DVs and 1,000 NDVs was based on the estimated prevalence of the primary medical and psychiatric outcome measures of the study. Although sample size calculations were not performed a priori for pulmonary function abnormalities, the achieved sample size provided 80% power to detect prevalence differences of 6.0% for NPF (assumed prevalence among NDVs, 64.3%); 4.5% for NRAO (assumed prevalence among NDVs, 18.0%); 3.5% for RLP (assumed prevalence among NDVs, 10.3%); 2.7% for SAO (assumed prevalence among NDVs, 6.0%); and 0.9% for RAO (assumed prevalence among NDVs, 0.9%).

The Fisher exact test and \(t\) tests for categorical and continuous outcomes were used for comparisons of sociodemographic and military characteristics by veteran deployment status. Because a complex stratified random sampling schema was used to select participants, all subsequent analyses were carried out using the SUDAAN statistical software, version 8.0 (Research Triangle Institute, Research Triangle Park, NC). Calculations were performed with SAS statistical software, version 8.0 (SAS Institute, Cary, NC).
The prevalence of physician visits for pulmonary complaints was similarly low for both groups of veterans (about 3%), as was the prevalence of self-reported and physician-diagnosed asthma. A comparison of the types of pulmonary medications taken by DVs and NDVs did not reveal any significant differences (data not shown). Overall, the prevalence of pulmonary medication use was very low, ranging from 2.7% to 3.8%.

The patterns of pulmonary function abnormalities among DVs and NDVs were not statistically different (Figure). Pulmonary function was normal in approximately 64% of both DVs and NDVs, 16% to 18% of both DVs and NDVs had NRAO; 10% to 12.2% had RLP; 6% to 6.7% had SAO; and the remaining 0.9% to 1.3% had RAO. Deployed veterans who were theoretically exposed to toxic fumes at Khamisiyah had no increased prevalence of pulmonary function abnormalities compared with DVs who were not exposed or with NDVs.

Phase I (mail) and phase II (telephone survey) of the National Health Survey of Gulf War Era Veterans and Their Families concluded that DVs were statistically significantly more likely than NDVs to report having been evaluated in a clinic, hospitalized at least once in the previous year, and being functionally impaired. Furthermore, deployment was associated with a significantly higher self-reported prevalence of bronchitis and asthma than nondeployment. Thus, the higher prevalence of respiratory symptoms reported by DVs confirmed the importance of performing a detailed face-to-face evaluation.

The analysis of the primary outcomes of the present phase III study indicated that Gulf War I deployment was not associated with a significantly increased risk of obstructive airway disease. We found no relationship between deployment to the Gulf War I conflict or estimated exposure to toxic chemicals released by the Khamisiyah explosion and the amount of current bronchodilator or to corticosteroid metered-dose inhaler use or to any objective measurement of a pulmonary condition, either obstructive (NRAO, RAO, or SAO) or restrictive (RLP).
Other investigators have reported that self-reported asthma and bronchitis are increased among Gulf War veterans exposed to oil well fires. However, in these cases, exposures were determined partially by mathematical modeling, which is subject to error, and outcomes were determined by structured telephone interviews. In another case-control study in which the health of 873 Gulf War veterans exposed to oil well fire smoke was compared to that of 2464 nonexposed controls, an increase in physician-diagnosed asthma was identified in the exposed group, but no etiologic association between the oil fires and the development of asthma could be proven.

Although DVs were statistically more likely to self-report a history of smoking and wheezing than were NDVs, objective comparisons of reported physician visits for pulmonary complaints, pulmonary hospitalizations, numbers of documented episodes of asthma, bronchitis, or emphysema, and pulmonary medications between DVs and NDVs did not reveal any differences. The patterns of PFT distribution among DVs and NDVs were identical. Given the time necessary for nonreversible obstructive lung changes to develop, it would be unlikely to find evidence of chronic obstructive pulmonary disease, a condition that usually develops after the age of 50 years, in this population of relatively young individuals. Thus, it is not surprising that no significant differences were found in the prevalence of NRAO between DVs and NDVs. The increased prevalence of symptoms in DVs may be explained by psychological factors related to greater stress; data related to this hypothesis will be presented separately.

Finally, we found no effect of deployment on the prevalence of RLP 10 years later. Although we did not obtain chest radiographs or measure oxygen saturation, the absence of reductions in vital capacity on objective evaluation make a higher prevalence of interstitial lung disease unlikely. In summary, our findings do not support the hypothesis that Gulf War deployment in 1990-1991 resulted in an increased prevalence of objectively measured, clinically significant pulmonary abnormalities in DVs 10 years later.

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Figure. Distribution of pulmonary function abnormalities in Gulf War Veterans. DVs indicates deployed veterans; NDVs, nondeployed veterans; NPF, normal pulmonary function; NRAO, nonreversible airway obstruction; RLP, reversible lung physiology; SAO, small airway obstruction; RAQ, reversible airway obstruction.

REFERENCES