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A Case-Control Study of Asthma among U.S. Army Gulf War Veterans and Modeled Exposure to Oil Well Fire Smoke

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Objective: Thousands of American troops were exposed to oil well fire smoke during the Persian Gulf War, but the actual impact of this on their health is unknown. To assess the potential association between physician-diagnosed asthma and objective estimates of oil fire smoke, we conducted a case-control study of Army Gulf War veterans. Methods: Subjects were participants in the Comprehensive Clinical Evaluation Program. Cases had physician-diagnosed asthma; controls were selected from the population of noncases. The two estimates of exposure were cumulative exposure and number of days at high levels. Results: A total of 873 cases and 2,464 controls were included. Significant associations were observed between asthma and both estimates of exposure, with an adjusted odds ratio of 1.4 (95% confidence interval = 1.1–1.8) for both the highest levels of cumulative exposure and days exposed to high levels. A dose response was observed for both exposure measures. Conclusions: We found significant associations between asthma and oil fire smoke exposure. Because much of the medical history was not available, an etiological association cannot be determined from this study, and additional research is needed.

Introduction

In February 1991, shortly before the beginning of the ground phase of the Persian Gulf War, Iraqi forces set fire to approximately 605 oil wells. The dramatic photographs and reports of the fires and smoke raised health concerns for the thousands of potentially exposed U.S. troops. In 1992, the 102nd Congress responded to this concern by passing provisions of Public Law 102-190 (the National Defense Authorization Act for Fiscal Years 1992 and 1993) that required the Secretary of Defense to establish a registry of military personnel who were exposed to the fumes of oil well fires. This registry is to contain descriptions of exposure for each individual. This law also requires the Secretary of Defense to annually report the results of all ongoing studies to determine the health consequences of exposure to the oil well fires.

In the years after the Gulf War, the Department of Defense initiated a number of programs to address the concerns of veterans and Congress. The Comprehensive Clinical Evaluation Program (CCEP) organized and coordinated the medical evaluation of active duty Gulf War veterans.[1–3] The U.S. Army Center for Health Promotion and Preventive Medicine, in conjunction with the U.S. Armed Services Center for Unit Records Research, developed a geographic information system to locate and track military units in the theater of operations.[4] Through a collaborative effort, the National Oceanic and Atmospheric Administration's Air Resources Laboratory and the Center for Health Promotion and Preventive Medicine's Deployment Environmental Surveillance Program developed a model of the oil well fire smoke.[5,6]

In its interim report of February 1996, the Presidential Advisory Committee on Gulf War Veterans' Illnesses noted the potential utility of geographic information system technologies and meteorological modeling in conducting epidemiological studies to evaluate the possible health effects of exposure to oil fire smoke.[7] In its final report of 1996, the Institute of Medicine commented on the value of using the integrated geographic information system to estimate exposure to oil well fire smoke.[8]

Although human health risk assessments have been conducted,[4] there is little epidemiological information evaluating the actual impact of the fires on the health of military personnel. No official or peer-reviewed published reports have been identified that evaluate the prevalence or incidence of asthma during the war. However, a letter from the Pulmonary and Respiratory Therapy Consultant to the Surgeon General (Army) to the Chief of the Medical Corps provides some limited information (Y.Y. Phillips, unpublished data). The letter reports that approximately 200 soldiers were evacuated from the theater of operations with a diagnosis of asthma and that 13% of these were for their first occurrence.

In 1993, the Department of Defense published a report to Congress regarding exposure to smoke from the oil fires.[9] One section of this report provided an epidemiological assessment of acute effects among approximately 2,700 Marines assigned to three groups. Each group had a different level of exposure, in terms of intensity and duration, to the oil fire smoke. The Marines were interviewed via questionnaire between March 14 and 31, 1991, while the fires were still burning. Group I, which had the highest exposure to smoke, had a significantly higher prevalence of self-reported wheezing (odds ratio [OR] = 3.1, 95% confidence interval [CI] = 1.9–5.0), cough (OR = 1.5, CI = 1.2–2.0), runny nose (OR = 1.5, CI = 1.2–1.9), and sore throat (OR = 1.5, CI = 1.1–2.0) than did group III, which had the lowest exposure (all OR values were adjusted for smoking, history of respiratory disease, and receipt of influenza vaccine). Within groups, a smaller proportion of smokers than nonsmokers complained of oil smoke irritation.

Respiratory diseases in general and asthma specifically were relatively common primary diagnoses among CCEP participants.[1,3] A primary diagnosis involving the respiratory system was reported for 6.8% of participants, whereas 17.5% had a primary or secondary diagnosis involving the respiratory sys-

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tem. Asthma, unspecified (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 493.9) was reported as a primary diagnosis for 2.2% of the participants (prevalence as a secondary diagnosis was not reported). The prevalence of asthma in the general population has been estimated to be from 4 to 8%.[10]

Because asthma can be induced or aggravated by exposure to respiratory irritants,[11] including particulate matter of <10 μm in diameter,[12,13] we selected it as the end point for this study. The epidemiological study of asthma in an occupational setting is challenging, as noted by Cullen[14]: "The endpoint is surprisingly elusive; host factors, as yet undefined, play havoc with dose-response relations and. . . the disease itself frequently impacts exposure through job selection and behavior."

The population of American service members deployed to the Gulf War was large enough (approximately 700,000) for there to be substantial numbers of genetically susceptible individuals exposed to a wide range of respiratory agents, particularly smoke from the oil well fires. This study explored the possibility that modeled exposure to oil well fire smoke was associated with receiving a physician-assigned asthma diagnosis among participants of the CCEP. If such an association could be demonstrated, it would provide a basis for subsequent studies to determine whether a causal relationship exists between exposure to the smoke from the oil well fires and asthma.

Methods

Study Population

The majority of military personnel in the vicinity of the oil well fires were from the Army and Marine Corps. Unit location information was available at the company level (approximately 130 persons per company) for Army units but only at the battalion level (four to six companies per battalion) for Marine Corps units. Because the location data were more precise for Army companies, only Army personnel were included in the study.

All study subjects were selected from the population of active component Army (active duty or regular Army) personnel who served in Operation Desert Shield/Storm (based on the Defense Manpower Data Center Gulf War Registry) and who were evaluated in the CCEP. These examinations were conducted at Department of Defense medical facilities by military physicians or civilian physicians employed by the military. Only study subjects with valid unit identification codes and units of assignment were selected. CCEP examinations took place three3 to six6 years after potential exposures occurred during the war.

Establishing the diagnosis of asthma in a clinical setting can be problematic, and establishing the diagnosis for purposes of epidemiological study can be even more troublesome.[15] Some asthma researchers have used responses to questionnaires asking respondents if they "wheeze ever," and "asthma ever diagnosed" is often used.[16,17] For this study, we used a physician-assigned diagnosis of asthma (ICD-9-CM codes 493 and 493.91) to define cases. Additional information on the CCEP is available elsewhere.[1,3] The diagnoses were based on patient complaints, signs and symptoms, and a physical examination, but the accuracy of this diagnosis could not be ascertained from the available data. Although physicians could refer subjects for special studies, data related to diagnostic criteria and laboratory evaluations were not available. Medical records from before the Gulf War were not available for examination, and the presence or absence of asthma before exposure could not be determined for this study. Therefore, these diagnoses could reflect new disease or exacerbated asthma. Cases may have had other diagnoses in addition to asthma.

Controls were randomly selected from those CCEP participants who did not qualify to be cases. Controls were also restricted to those who had no respiratory system diagnoses (ICD-9-CM codes 460 to 519), no respiratory system-related symptoms, signs, and ill-defined conditions diagnoses (ICD-9-CM codes 786.0 to 786.9), and no respiratory system-related symptoms or complaints. Three controls were selected for each case, and there were no matching criteria.

Questionnaire Data

Demographic information was obtained from the Defense Manpower Data Center Gulf War Registry, as used in the CCEP database. During the CCEP evaluation, participants were asked about self-reported oil well fire smoke exposure (yes/no) and about smoking history (current/former/never). None of the responses to any CCEP questions have been validated by any external or objective assessment.

Unit Location Data

We used Department of Defense personnel records maintained by the Defense Manpower Data Center to determine each study subject's unit and dates of service. The U.S. Armed Services Center for Unit Records Research constructed a database containing the geographical locations of military units on a daily basis. For Army units, locations were tracked at the company level. Study subjects assigned to units that could not be tracked were excluded from further analysis. All reported coordinates for each company were used. Sometimes, there were multiple locations on a single day, resulting in different modeled exposures for that company. If the coefficient of variation (100% $\times$ SD/mean) in the modeled exposures for a single subject was >25%, the subject was excluded from further analysis.

Oil Well Fire Smoke Model

The National Oceanic and Atmospheric Administration Air Resources Laboratory (Silver Spring, Maryland) constructed an atmospheric advection and diffusion model. This model evaluated oil fire smoke (i.e., soot) by predicting spatially (resolution of 15 km) and temporally (24-hour average) concentrations at 2 m above the terrain.[5,6] The model was developed using input from satellite imagery and ground station air-monitoring data. Emission rates were developed using extinguishment chronologies developed by the National Oceanic and Atmospheric Administration Arabian Gulf Program Office (J. McQueen and R. Draxler, personal communication, June 1998) and Kuwaiti crude oil composition data. More data on the oil fires is available from Husain.[18]

Most of the particulate matter was between 0.1 and 0.8 μm in diameter. The total mass of suspended particulates in the near-field plumes typically ranged from 1 to 5 mg/m^3.[19] Black smoke fires constituted 60 to 65% of the oil well fires, and elemental carbon was the primary carbonaceous particulate component of these. White plumes contained little soot. Other substantial

components of the plumes included sodium and calcium salts and sulfates.[18,19] The composite "super plume" was composed of approximately 30% salts, 8% sulfates, 30% organic compounds, and 15% to 20% soot, with the balance not specified.[20] Thus, because the models considered only soot, the total suspended particles may have been at levels five to seven times as great as the estimates used in this study.

Based on samples collected while the wells were still burning, the fires produced particles of a size (0.1–0.8 μm) that would be deeply inspired and likely would be retained in the lungs. Estimates of total suspended particulates of <3.5 μm in diameter in plumes were 840 $\mu g/m^3$ 20 km downwind of the fires and 210 $\mu g/m^3$ 160 km downwind.[20] Hobbs and Raadke[20] estimated the daily soot emitted to be 13 times that emitted from all combustion sources in the United States.

Geographic Information System Analysis

A geographic information system (Oracle Relational Database Management System (Redwood Shores, California) and Intergraph Modular GIS Environment software (Huntsville, Alabama) on an NT-based Intergraph Corporation interserve multiprocessor computer (Huntsville, Alabama) was used to link the spatially and temporally referenced military unit location data with modeled oil well fire smoke concentrations for each day of deployment.

Exposure Estimates

For each unit, we used the nearest modeled data point to define exposure. Exposure was estimated from the one point estimate for every 24-hour period and was expressed in terms of concentration duration (i.e., mg/m^3/day and $\mu g/m^3$/day). Two measures of modeled exposures to the smoke were used in this study.

The first measure was an estimate of cumulative smoke exposure and was defined as the sum of the estimated concentration for all days that each subject was in theater (mg/m^3/day). In addition to being analyzed as a continuous variable, cumulative exposure was categorized. The referent exposure was <0.1 mg/m^3/days, the intermediate levels were ≥0.1 and <1.0 mg/m^3/day, and the highest level as ≥1.0 mg/m^3/day.

The second measure was the number of days the subject was exposed to levels of 65 $\mu g/m^3$ or higher. The cutoff point of 65 $\mu g/m^3$ was selected because it is the National Ambient Air Quality Standard for 24-hour particulate matter of <2.5 μm diameter.[21] In addition to being analyzed as a continuous variable, this measure was grouped with 0 days as the referent exposure, 1 to 5 days as the intermediate level, and 6 to 30 days as the highest exposure.

Both of theses measures were also considered as dichotomous variables (any vs. none).

Data Analysis

Univariate associations between asthma and all independent variables, including demographic variables, CCEP questionnaire data, and modeled exposures, were evaluated with the OR as the measure of association. OR values > 1.0 indicate a positive association between asthma and the predictor variable. If the 95% CI includes the value of 1.0, the association is not statistically significant at the 0.05 level. p values are presented for some comparisons. Multivariate analyses to calculate adjusted ORs were conducted with logistic regression using the SPSS statistical program package. Subjects with any data elements missing were excluded from multivariate analyses. Associations between exposure estimates were evaluated with the Spearman coefficient of correlation for continuous variables and the κ statistic for categorical variables.

Results

We initially identified 950 asthma cases and 2,850 controls for consideration. Of those initially considered, 873 (92%) asthma cases and 2,464 (86.5%) controls had adequate location data and therefore were selected for study inclusion. Selected data elements were missing for some subjects, so totals presented by various characteristics vary. The geographic locations over time of military units with and without study subjects were similar. The demographic characteristics of cases and controls are listed in Table I, along with the univariate associations of those characteristics with receiving a diagnosis of asthma. Men were less likely than women to receive a diagnosis of asthma, with an OR of 0.67. Soldiers aged 19 to 24 years were slightly more likely to be diagnosed with asthma than were all older age groups. No racial groups had a significant association with a diagnosis of asthma. Officers were less likely to receive a diagnosis of asthma than were enlisted personnel. The OR for former smokers was not different from 1.0, but current cigarette smok-

TABLE I

UNIVARIATE ASSOCIATIONS BETWEEN ASTHMA AND DEMOGRAPHIC CHARACTERISTICS

Variable and Level	Number of Cases	Number of Controls	OR (95% CI)
Sex			
Female	133	264	1.00 (referent)
Male	739	2,200	0.67 (0.53–0.84)
Age group at time of evaluation (years)			
19–24	262	662	1.00 (referent)
25–29	231	646	0.90 (0.73–1.12)
30–34	202	608	0.84 (0.67–1.05)
≥35	161	520	0.78 (0.62–0.99)
χ^2 for trend = 5.10, p = 0.024			
Race/ethnicity			
White	439	1,225	1.00 (referent)
Black	311	909	0.95 (0.80–1.13)
Hispanic	50	127	1.10 (0.77–1.57)
Other	73	203	1.00 (0.74–1.35)
Rank			
Enlisted	799	2,169	1.00 (referent)
Officer	66	246	0.73 (0.54–0.98)
Cigarette smoking			
Never	499	1,327	1.00 (referent)
Former	186	461	1.07 (0.87–1.32)
Current	188	676	0.74 (0.61–0.90)
Self-reported oil well fire smoke exposure			
No	111	443	1.00 (referent)
Yes	634	1,626	1.56 (1.23–1.97)

TABLE II

UNIVARIATE ASSOCIATIONS BETWEEN ASTHMA AND MEASURES OF SMOKE EXPOSURE

Categories	Cases	Controls	OR (95% CI)
Cumulative exposure mg/m^3/day			
<0.1	172	592	1.00 (referent)
≥0.1 to <1.0	292	829	1.21 (0.97–1.51)
≥1.0	273	670	1.40 (1.12–1.76)
Any vs. none			1.30 (1.06–1.58)
χ^2 test for trend = 9.04, p = 0.003			
Days with exposure ≥65 μg/m^3			
0	215	723	1.00 (referent)
1–5	270	745	1.22 (0.99–1.50)
6–30	218	495	1.48 (1.19–1.85)
Any vs. none			1.32 (1.10–1.60)
χ^2 test for trend = 12.26, p = 0.0005			

ers were significantly less likely to receive a diagnosis of asthma than were never smokers, with an OR of 0.74.

There was an OR of 1.56 for asthma among those self-reporting exposure to oil well fires. Although subjects self-reporting oil smoke exposure had significantly higher modeled exposures than did those with no reported exposures, reliability between the self-reported and modeled exposures was low. The κ correlation for the comparison of self-reported exposure with cumulative exposure was 0.13 and 0.12 for days exposed to ≥65 μg/m^3. The two modeled exposures, cumulative and days with high concentration, were correlated, with a Spearman correlation coefficient of 0.84 between ungrouped measures.

As seen in Table II, statistically significant univariate associations were found between asthma and both exposure estimates. For cumulative exposure, the wereOR was increased significantlyelevated for both the intermediate and the highest exposure groups as well as for those with any exposure compared with none. There was a significant linear trend between total exposure and asthma, indicating a potential dose-response relationship. Similar patterns were seen for those with 1 to 5 days of exposure to high smoke levels and those with 6 to 30 days of exposure and when those with any days of exposure were compared to those with none. There was a significant linear association between days exposed and asthma.

The association between asthma, modeled exposures, and smoking status (never, former, and current) was explored further with stratified analyses, as shown in Table III. The highest category of cumulative exposure and number of days exposed to ≥65 μg/m^3 were significant predictors of asthma for never smokers and former smokers but not for current smokers.

Adjusted ORs for modeled exposure are presented in Table IV. The adjusted ORs were very similar to those found by univariate analysis. When considered as a continuous variable, the adjusted OR (and 95% CI) for cumulative exposure was 1.08 (p < 0.05) and 1.03 (p < 0.05) for days exposed to ≥65 μg/m^3.

Discussion

This case-control study of physician-diagnosed asthma and objective estimates of exposure to oil well fire smoke found statistically significant associations for two measures of modeled smoke exposure, and dose-response relationships were observed for both measures of exposure. Significant linear trends were observed by univariate analyses (Table II), and when exposures were considered as a continuous variable, significant adjusted ORs for each unit increase of exposure were noted (Table IV). ORs increased consistently with increased exposure in all univariate and multivariate comparisons (Tables II, III [except for current cigarette smokers], and IV).

This study demonstrates the potential use of geographic information system technology in conducting environmental epidemiological studies, as well as the linking of databases originally created for different purposes, but it also demonstrates its limitations. We believe this to be the first epidemiological study of Gulf War veterans to use objective assessments of exposure and physician-diagnosed outcome. There have been several population-based epidemiological studies of Gulf War veterans, some of whichsome have used outcomes based on physician-assigned diagnoses,[22–25] whereas others have used self-reported complaints.[26,27] Those studies that used physician-assigned diagnoses used no measure of exposure other than deployment to the theater of operations,[22–25] whereas those that used self-reported complaints also used self-reported exposures.[26,27] None of the studies to date have used objective measures to specific environmental exposures.

Because the CCEP population is self-selected, the findings of this study may not be generalizable to the broader population of Gulf War veterans. Because the examinations took place three3 to six6 years after the war and the pre-exposure asthma status of the subjects cannot be determined, an etiological association between the modeled exposures and the diagnoses cannot be assumed from these data. In addition, no information was available on potential exposures that may have occurred between the Gulf War and the CCEP evaluation. There is evidence that exposures to high concentrations of small-diameter particulate

TABLE III

ORS (95% CI) FOR ASTHMA BY SMOKING STATUS

Categories	Never Smoked	Former Smoker	Current Smoker
Cumulative exposure mg/m^3/day			
<0.1	1.00 (referent)	1.00 (referent)	1.00 (referent)
≥0.1 to <1.0	1.31 (0.98–1.77)	1.27 (0.75–2.16)	1.00 (0.71–2.16)
≥1.0	1.43 (1.06–1.94)	1.73 (1.04–2.90)	1.05 (0.64–1.72)
Days with exposure ≥65 μg/m^3			
0	1.00 (referent)	1.00 (referent)	1.00 (referent)
1–5	1.24 (0.99–1.64)	1.54 (0.95–2.51)	0.92 (0.63–1.34)
6–30	1.35 (1.00–1.82)	2.02 (1.23–3.34)	1.29 (0.79–2.09)

TABLE IV

ADJUSTED ORS FOR ASSOCIATIONS WITH MEASURES OF SMOKE EXPOSURE

Categories	Adjusted OR (95% CI)
Cumulative exposure mg/m^3/day	
<0.1	1.00 (referent)
≥0.1–<1.0	1.24 (1.00–1.55)
≥1.0	1.40 (1.11–1.75)
Continuous	1.08 (1.01–1.15)
Days with exposure ≥65 μg/m^3	
0	1.00 (referent)
1–5	1.22 (0.99–1.51)
6–30	1.41 (1.12–1.77)
Continuous	1.03 (1.01–1.05)

OR was adjusted for sex, age, race/ethnicity, rank, smoking history, and self-reported exposure.

matter is associated with asthma,[11–13] although in this study it was not possible to distinguish between new cases and aggravated or reactivated cases of asthma.

Different patterns of association with the modeled exposures were observed between nonsmokers and former smokers compared with current smokers. The reasons that current smokers appear to be at lower risk of an asthma diagnosis and why the association between the modeled exposures and asthma is weakest in this group cannot be readily addressed from the existing data. We can speculate that the modeled exposures were trivial relative to the daily particulate exposures routinely experienced by current smokers, or that current smokers have suppressed respiratory responses to irritants, or that smokers represent a group that is innately nonsusceptible to developing asthma (the "healthy smoker" effect). It is possible that former smokers represent a more susceptible group, and thus are more likely to experience respiratory symptoms and to subsequently stop smoking, because their ORs were slightly but consistently higher than those of nonsmokers (Table III).

There are several potential sources of error in this study, both in measures of outcome and in measures of exposure. If these potential errors were nondifferential (exposure errors equal for cases and controls, outcome errors equal for exposed and nonexposed), then each source waswould likelyto bias the results toward the null. That is, the observed effects would be likely to underestimate the true effects.[28–30]

Potential outcome errors include misclassifying nonasthmatics as cases (false positive) and asthmatics as controls (false negative). The existing data are not adequate to estimate the proportion of cases misclassified. However, the use of physician-assigned diagnoses provides some degree of certainty regarding the classification. It is not possible, however, to determine the date of onset, duration, or severity of the asthma. Misclassification of asthmatics as controls was probably less likely, because subjects with any evidence of respiratory problems were excluded from being controls. Because diagnoses were made before and independently of exposure estimates, any outcome misclassification is likely to be nondifferential on exposure.

Errors in exposure estimation could have occurred at several points and may have been more likely than outcome errors. Although efforts were made to exclude from analysis soldiers whose locations were obviously in error (especially as a result of multiple locations being reported for a given day), it is not possible to evaluate the accuracy of the existing unit location data. Error could also result if, for days for which no location was available, exposures to smoke actually occurred. One data point for location and particulate concentration per 24-hour period was used, although the actual location of the individual and the smoke concentration may have varied over the period. Exposure error could also result from inaccuracies in the plume models used.[5,6] Although the Institute of Medicine recommended that the plume models be validated,[8] there is no existing method to externally validate the model, at least at the level of the individual. The closest agreement between the modeled and measured emissions at selected sites was 200 km or more downwind, where concentrations were lowest.[5] Because exposures were estimated independently of case or control status, exposure error is probably nondifferential on outcome.

A selection bias may have occurred if subjects who thought they were exposed to the plume differentially entered the CCEP with complaints compatible with asthma. Given the low level of agreement between the self-reported and modeled exposure, this may not have introduced substantial bias, but it was not possible to evaluate the extent to which this may have occurred.

In conclusion, the low to moderate ORs observed for the modeled exposures do not indicate a strong association between oil well fire smoke and risk of asthma, and the observed associations do not explain a large part of the variability of the outcome. When the observed ORs are considered in light of the substantial opportunity for misclassification, the findings suggest an association between objective estimates of exposure to oil well fire smoke and the risk of asthma diagnosis among Army CCEP participants. These findings are not definitive, and additional studies are required before an etiological association can be determined. By examining the medical records of study subjects, and possibly through interviews, it may be possible to better ascertain the initial onset, duration, and exacerbation of asthma and therefore better understand the potential association with oil fire smoke exposure.

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