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ABSTRACT

In 1991, US Army personnel were potentially exposed to chemical warfare agents following the demolition of the Khamisiyah ammunition depot in Iraq. We conducted three related investigations concerning morbidity and mortality. First, we analyzed data from 5,555 Army veteran respondents to the VA's 1995 National Health Survey of Gulf War Era Veterans and their Families to study the association between potential exposure to chemical agents and self-reported morbidity. Potential exposure status was determined from Department of Defense (DoD) data known as the 2000 plume model. Second, we resurveyed a sample of roughly 1,200 respondents to the original survey to obtain self-reported morbidity after some of these original respondents had been notified by DoD of possible exposure to chemical agents. Comparing pre- and post-notification morbidity allowed us to study the association of notification and morbidity. Neither possible exposure nor notification of possible exposure were unduly associated with morbidity. Third, we examined the association between mortality among some 351,000 deployed Army veterans and potential exposure. We found a roughly two-fold excess of deaths due to brain cancer in the exposed group, representing an excess of 12 deaths in roughly 100,000 subjects in a 10-year period.

The results of our research were published in three papers in two peer-reviewed journals.

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Introduction

In March 1991, demolition of the Khamisiyah ammunition depot was carried out. As a result, troops may have been exposed to chemical warfare agents. Representatives of the United Nations Special Commission (UNSCOM) inspected the Khamisiyah site and detected the presence of sarin and cyclosarin. On June 21, 1996, the Department of Defense (DoD) released a statement saying that US personnel had destroyed the depot and that chemical warfare agents may have been destroyed (1).

DoD subsequently undertook efforts to determine possible exposure to chemical warfare agents. Using data on agent dispersion and meteorological conditions at the time, DoD personnel developed a "1997 plume model" and later a "2000 plume model" that each yielded a hazard area of potential exposure. Troops whose units were located in the hazard area can be considered potentially exposed to chemical warfare agents. DoD also made efforts to notify personnel who were thought to be in a hazard area of their potential exposure.

Our current study examined the association between 1) potential exposure and morbidity; 2) between notification of potential exposure and morbidity; and 3) between potential exposure and mortality. The cohorts for each of the three investigations are different and will be described below. The goal of the three investigations was to determine whether potential exposure to chemical agents following the Khamisiyah detonation, or notification of such exposure, was associated with subsequent ill health.

Body

Materials and Methods

The subjects for these three studies were drawn from the population of Army veterans deployed to the 1991 Gulf War. For the study of the association between potential exposure and morbidity, subjects were respondents to the 1995 National Health Survey of Gulf War Era Veterans and Their Families. For the study of the association between notification and morbidity, a subsample of respondents to the 1995 survey were resurveyed in 2000. In both cases, morbidity items came from the national survey (2).

For the study of potential exposure and mortality, all deployed Army Gulf War veterans, numbering some 351,000, were followed. Mortality was determined using Department of Veterans Affairs (VA) and Social Security Administration (SSA) records to establish fact of death, and VA and National Death Index records were used to obtain cause of death data.

This study was conducted with the advice of an expert panel, chaired by Dr. Barbara Hulka. Human Subjects review and approval of the protocol, the questionnaire, and associated materials was given by the National Academies' and the Army's Human Subject s Review Committees.

Analysis and Reporting

Rates of various health outcomes in the potentially exposed and unexposed groups were compared. The primary outcomes of interest included general health,

activity limitation days, clinic visits, a list of some 31 medical conditions, a list of some 48 symtoms, and posttraumatic stress disorder, ascertained using a standard scale. Risk estimates for these outcomes were calculated using Mantel-Haenszel statistics adjusted for covariates such as age in 1991, sex, race, marital status, military rank, and National Guard or Reserve status.

With regard to self-reported morbidity and exposure, we looked at a total of 86 health measures and found little association between these measures and possible exposure. Regarding the 31 self-reported medical conditions (e.g., arthritis, diabetes, hypertension), only two significant associations were seen. Regarding the 47 self-reported severe symptoms (e.g., headache, shortness of breath, fever or chills), only two significant associations were seen.

With regard to mortality, we found a significantly higher rate of deaths due to brain cancer in the possible exposed group. The roughly two-fold excess represented an estimated 12 excess brain cancer deaths among roughly 100,000 possibly exposed Army personnel over the course of a 10-year follow-up.

Key Research Accomplishments

During this study, the following key research accomplishments were achieved:

- the exposure cohort and control cohorts were selected for each of the three studies;
- vital status was obtained for the mortality cohort using VA and SSA records;
- death certificates were obtained from VA records and cause of death data from the National Death Index;

- data from the VA's 1995 National Survey of Gulf War Era Veterans were obtained and the morbidity cohort constructed;
- a subsample of respondents to the 1995 survey was selected;
- Human Subjects approval for conduct of the study was received from The National Academies' and Ar my Human Subjects Committees.
- the resurvey was conducted with an overall response rate of approximately 72%;
- data from medical records associated with brain cancer deaths were obtained and analyzed;
- the data were analyzed and a three journal articles were published in peer-reviewed journals.

Reportable Outcomes

Three reports were published in peer-reviewed scientific journals (3, 4, 5).

Conclusions

We found little evidence of an association between self-reported morbidity and either possible exposure or notification of possible exposure. We did find evidence of a statistically significant association between possible exposure and subsequent death due to brain cancer. The roughly two-fold excess represented an estimated 12 excess brain cancer deaths among roughly 100,000 possibly exposed Army personnel over the course of a 10-year follow-up. These results will be of interest not only to researchers and participants in the original program, but may also be relevant to those studying health effects following chemical agent exposures of a similar nature. Copies of the published article have been provided to the Army.

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Mortality in US Army Gulf War Veterans Exposed to 1991 Khamisiyah Chemical Munitions Destruction

Tim A. Bullman, MA, Clare M. Mahan, PhD, Han K. Kang, DrPH, William F. Page, PhD

Objectives. We investigated whether US Army Gulf War veterans who were potentially exposed to nerve agents during the March 1991 weapons demolitions at Khamisiyah, Iraq, are at increased risk of cause-specific mortality.

Methods. The cause-specific mortality of 100 487 exposed US Army Gulf War veterans was compared with that of 224 980 unexposed US Army Gulf War veterans. Exposure was determined with the Department of Defense 2000 plume model. Relative risk estimates were derived from Cox proportional hazards models.

Results. The risks of most disease-related mortality were similar for exposed and unexposed veterans. However, exposed veterans had an increased risk of brain cancer deaths (relative risk [RR] = 1.94; 95% confidence interval [CI] = 1.12, 3.34). The risk of brain cancer death was larger among those exposed 2 or more days than those exposed 1 day when both were compared separately to all unexposed veterans (RR = 3.26; 95% CI = 1.33, 7.96; RR = 1.72; 95% CI = 0.95,3.10, respectively).

Conclusions. Exposure to chemical munitions at Khamisiyah may be associated with an increased risk of brain cancer death. Additional research is required to confirm this finding. (*Am J Public Health.* 2005;95:1382–1388. doi:10.2105/AJPH.2004.045799)

On March 4 and 10, 1991, combat engineer and explosive ordnance disposal units of the US Army XVIII Corps destroyed 2 large Iraqi weapons caches at Khamisiyah, Iraq. In October 1991, March 1992, May 1992, and May 1998, representatives from the United Nations Special Commission inspected Khamisiyah and detected the existence of sarin and cyclosarin in both intact and damaged rockets in the bunker and pit. Military personnel who were possibly exposed to chemical warfare agents at Khamisiyah were identified by environmental and climatological modeling of the plume dispersion.

Sarin is a toxic nerve agent produced for chemical warfare. Sarin can be inhaled or absorbed via the mucous membranes, skin, or eyes, and at sufficient dosage it can cause convulsions and death.[1] Acute sarin exposure produces a well-characterized acute cholinergic reaction, and doses sufficient to produce an acute reaction have been associated with persistent health effects such as fatigue, vision problems, and headaches.[1] There is no evidence that sarin is carcinogenic.[2]

Several studies have examined cause-specific mortality risks associated with Gulf War service by comparing the mortality of all Gulf War veterans to that of veterans who served in the military during the period of the Gulf War but did not serve in the Persian Gulf region.[3–5] Although reporting that Gulf War veterans were at increased risk for traumatic deaths, the studies did not find any increased risk of disease-related deaths. One of these studies assessed cause-specific mortality among Gulf War veterans who were considered exposed to nerve gas on the basis of the 1997 plume model.[4] When the mortality of 48 281 Gulf War veterans who were exposed to nerve gas at Khamisiyah was compared with that of 573 621 Gulf War veterans who were not exposed, there was no increased risk in either overall or cause-specific mortality among exposed veterans. Another study using the same exposure model found no unusual morbidity among exposed troops.[6]

To determine whether adverse health are outcomes associated with exposure to chemical agents released at Khamisiyah, we compared the mortality of all exposed US Army Gulf War veterans to that of unexposed US Army Gulf War veterans, using the 2000 plume model to assess potential for exposure.

METHODS

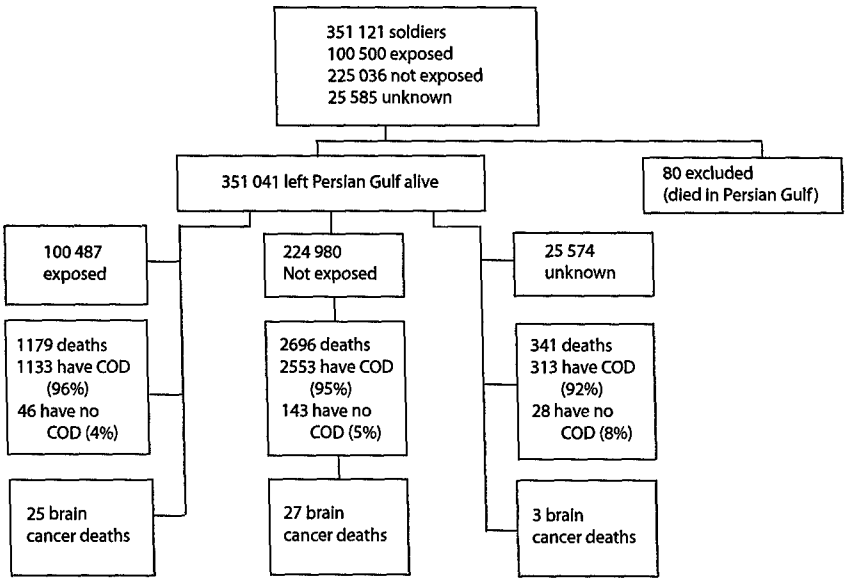
Identification of Study Subjects

The cohort for this study was selected in collaboration with the Office of the Special Assistant for Gulf War Illnesses, the Deployment Environmental Surveillance Program of the US Army Center for Health Promotion and Preventive Medicine, and the Environmental Epidemiology Service of the Department of Veterans Affairs.

We used the 2000 plume model to provide exposure status for 351 121 army personnel deployed to the Persian Gulf during the Gulf War (August 1990 to March 1991). Of these veterans, 80 were determined to have died in the Gulf and were excluded from this analysis, leaving a total of 351 041 (Figure 1). Among these veterans, 100 487 were considered exposed and 224 980 were considered unexposed. Exposure could not be determined for 25 574 veterans, because of missing or invalid unit or service date information.

Exposure Determination

The 1997 plume model, the first model used to determine the potential for exposure to agents released at Khamisiyah, was developed by a joint team of Department of Defense and Central Intelligence Agency personnel. This model is described in detail on a Department of Defense Web site[7] and in a study assessing postwar morbidity of potentially exposed veterans.[6] The 1997 plume model used data collected from those who were present at the Khamisiyah demolitions and from reconstructed demolitions. Dispersion models were used to predict the transport and spread of chemical warfare agents according to simulated meteorologic conditions. The result was the generation of a simulated potential hazard area that varied in size and shape from March 10 to March 13, 1991. In 2000, the Department of Defense and the Central Intelligence Agency



Note. COD = cause of death. Exposure is based on the 2000 plume exposure model developed by the US Department of Defense.

FIGURE 1—Deaths identified through 2000 for exposed, unexposed, and exposure-unknown veterans who were present at the 1991 Khamisiyah chemical munitions destruction.

developed the 2000 plume model, a refined version of their 1997 model. The 2000 plume model is described by the Department of Defense on its Gulf War–related Web site. Our study relied on the 2000 model to determine the likelihood of exposure. The 2000 plume model includes several improvements over the 1997 model. Among the improvements are revised meteorologic models, a reduced amount of nerve agent released, the addition of cyclosarin toxicity data, and the deposition and degradation data. Another improvement is more precise information regarding the location of individual units in Iraq at the time of the 1991 demolitions. In the 1997 model, an individual's location was largely determined by the location of that person's battalion, whereas, in the 2000 model, an individual's location was determined by the company's location. Because a battalion consists of 500 to 900 soldiers and a company consists of only 100 to 200 soldiers, locating individuals at the company level is believed to be more precise than locating them at the battalion level. Unit locations were based on 855 000 recorded daily unit locations in the Gulf Theater. The extent to which this represents all locations for military personnel during the war is unknown.

Vital Status Determination and Cause of Death Data

Vital status follow-up for each veteran began on the date the veteran left the Gulf Theater alive and ended on the earlier of either the veteran's date of death or December 31, 2000. Follow-up ended on December 31, 2000, as sources used for vital status ascertainment were incomplete after that date. Vital status was ascertained in part using the Department of Veterans Affairs computer database known as BIRLS (Beneficiary Identification and Records Locator Subsystem). BIRLS identifies all veterans who are eligible for benefits, including death benefits. Veterans were also matched against a file of deaths reported to the Social Security Administration. An earlier study assessing the mortality of Gulf War veterans determined that when used together, the BIRLS and Social Security Administration files of deaths had an estimated reporting rate of 89% for Gulf-era veterans (95% confidence interval [CI]=83%, 97%).[3] Cause of death data were obtained from the National Death Index.

Military Service and Demographic Characteristics

Demographic and military service characteristics for each veteran were obtained from a Defense Manpower Data Center database. This database identifies military personnel who were serving in the Persian Gulf during the Gulf War. Available data included age, race, gender, dates of service, rank, unit component, unit name, unit identification code, and military occupational specialty code. In addition to exposure data (yes/no/unknown), the model also provided the number of days exposed, ranging from 1 to 4 days, and the days on which each veteran was in the plume footprint.

Statistical Methods

Unadjusted relative risks were calculated as crude death rates, with the numerator equal to the number of deaths and the denominator equal to the number of person-years a person is at risk of dying. Follow-up began on the date when a veteran left the Gulf Theater alive and ended on December 31, 2000, or the date of death, whichever came first. Adjusted relative risks (RRs) were calculated with standard SAS software for the Cox proportional hazards model to account for possible confounding and effect modification by selected covariates.[9] Covariates included exposure (yes or no), age at entry to follow-up, gender, race (White vs non-White), rank (enlisted vs officer or warrant officer), and unit component (active duty vs National Guard or Army Reserves). Cause-specific mortality risks were also calculated for those exposed 1 day and those exposed 2 or more days, each compared with all unexposed veterans. Finally, cause-specific mortality of exposed and unexposed veterans was compared with that of the US population with adjustment for age, race, gender, and calendar year.[10] The results were expressed as standardized mortality ratios (SMRs), or the ratio of observed deaths among veterans to the expected number of deaths as determined by the US population. Cause-specific mortality categories included all major diagnostic groupings as set forth in the *International Classification of Diseases, Ninth Revision (ICD-9)*.[11] Although many specific diagnoses were analyzed, only a few are presented in

tabular form here. Any relative risk was considered statistically significant when its 95% CI did not include 1.00.

RESULTS

We identified 1179 deaths among exposed veterans, 2696 deaths among unexposed veterans, and 341 deaths among those with missing exposure data (Figure 1). Cause of death was obtained for 1133 (96%) of the deaths among exposed veterans, 2553 (95%) of the deaths among unexposed veterans, and 313 (92%) of those with missing exposure data. The majority of exposed, unexposed, and exposure-unknown veterans were White (64.8%, 64.5%, and 65.9%, respectively) and male (89.3%, 90.9%, and 86.9%, respectively) (Table 1). For all 3 groups, the majority of non-Whites, 81% to 82%, were African Americans, followed by Hispanics, 14.8% to 15%. The average age in years at entry to follow-up was 27.7 for exposed, 27.2 for unexposed, and 28.2 for exposure-unknown veterans. All veterans served in the army, and most were of the enlisted ranks: 88.4% of exposed, 89.8% of unexposed, and 86.7% of exposure-unknown veterans. Finally, 85.7% of exposed veterans were exposed for only 1 day.

Table 2 compares the overall and cause-specific mortality of exposed veterans with that of unexposed veterans, adjusting for age at entry to follow-up, race, gender, unit component, and rank. The overall mortality of both exposed and unexposed veterans was the same (RR=0.97; 95% CI=0.91, 1.04). Exposure was also not associated with an increased risk in disease-related mortality (*ICD-9* 001–799) (RR=0.96; 95% CI= 0.86, 1.07). When we looked at specific diseases as well as major disease groupings, there was only 1 disease for which exposed veterans were at a statistically increased risk. Compared with unexposed veterans, exposed veterans had an almost twofold increased risk of brain cancer–related deaths (*ICD-9* 191, 192) (RR=1.94; 95% CI=1.12, 3.34). Although not presented in Table 2, other cause-specific deaths, both traumatic and disease-related, were examined; none were associated with exposure.

The mortality of veterans exposed 1 day and that of veterans exposed 2 or more days was compared separately with the mortality of all unexposed veterans, with adjustment for age at entry to follow-up, gender, race, rank, and unit component (Table 3). Neither those exposed 1 day nor those exposed 2 or more days were at increased risk for overall mortality when compared with all those unexposed (RR=0.97 and RR=0.96, respectively). The only increased risk in cause-specific mortality among exposed veterans was for brain cancer deaths. Compared with all unexposed veterans, the greater increased risk for brain cancer deaths among exposed veterans was for those exposed 2 or more days (RR=3.26; 95% CI=1.33, 7.96), whereas those exposed 1 day had a relative risk of 1.72 (95% CI=0.95, 3.10). A test of trend analysis indicated that the risk of brain cancer increases steadily as the length of exposure increases. With the exception of 4 days, a category consisting of 112 individuals, none of whom were brain cancer deaths, brain cancer death rates per 100 000 persons steadily increased with increased length of exposure: 0 days (unexposed)=11.97; 1 day= 22.05; 2 days=39.83; and 3 days=60.35. A regression analysis of these data yields an estimate of 12.2 additional deaths per 100 000 persons for each added day of possible exposure (95% CI=4.8, 19.7).

We also compared the cause-specific mortality of all unexposed veterans, all exposed veterans, and exposed veterans when stratified by the number of days exposed (1 day or 2 or more days) with that of the

TABLE 1— Khamisiyah, Iraq, 1991 Chemical Munitions Destruction Exposure Status for US Army Gulf War Veterans, by Selected Demographic and Service Characteristics

	All Exposed (n = 100 487), No. (%)	All Unexposed (n = 224 980), No. (%)	Exposure Unknown (n = 25 574), No. (%)[a]
Age in 1990			
≤21	23 421 (23.3)	56 509 (25.1)	4951 (19.4)
22-25	25 825 (25.7)	58 852 (26.2)	6795 (26.6)
26-31	24 364 (24.2)	54 982 (24.4)	6302 (24.6)
≥32	26 877 (26.8)	54 637 (24.3)	7526 (29.4)
Mean age in 1990, y	27.7	27.2	28.2
Race			
White	65 146 (64.8)	145 009 (64.5)	16 849 (65.9)
Non-White	35 341 (35.2)	79 971 (35.5)	8725 (34.1)
Gender			
Male	89 777 (89.3)	204 594 (90.9)	22 225 (86.9)
Female	10 710 (10.6)	20 386 (9.1)	3349 (13.1)
Rank			
Enlisted	88 802 (88.4)	202 093 (89.8)	22 161 (86.7)
Warrant officer	1862 (1.8)	4728 (2.1)	703 (2.7)
Officer	9823 (9.8)	18 159 (8.1)	2710 (10.6)
Unit Component			
Active	74 464 (74.1)	175 089 (77.8)	17 745 (69.4)
Guard	11 897 (11.8)	24 445 (10.9)	1011 (3.9)
Reserve	14 126 (14.1)	25 446 (11.3)	6818 (26.7)
Number of days exposed			
1	86 167 (85.7)		
2	12 551 (12.5)		
3	1657 (1.7)		
4	112 (0.1)		

Note. Exposure is to nerve gas as a result of weapons demolition. Exposure is based on the 2000 exposure model developed by the US Department of Defense.
[a]Exposure status could not be determined because of missing or invalid unit data.

TABLE 2—Cause-Specific Mortality Among Exposed US Army Gulf War Veterans at Khamisiyah, Iraq, in 1991 Compared With Unexposed Army Veterans

Underlying cause of death (*ICD-9*)	Exposed (n=100 487), No. (Rate[a])	Not Exposed (n=224 980), No. (Rate[a])	Relative Risks		
			Crude	Adjusted[b]	95% CI
All causes	1179 (12.22)	2696 (12.47)	0.98	0.97	0.91, 1.04
All diseases (001-799)	496 (5.14)	1093 (5.05)	1.02	0.96	0.86, 1.07
Infectious and parasitic disease (001-139)	29 (0.30)	56 (0.26)	1.16	1.16	0.74, 1.82
Malignant neoplasm (140-208)	184 (1.91)	391 (1.81)	1.06	0.97	0.82, 1.16
Colon cancer (153)	14 (0.15)	26 (0.12)	1.25	1.17	0.61, 2.25
Pancreatic cancer (157)	10 (0.10)	24 (0.11)	0.91	0.82	0.39, 1.73
Lung cancer (162)	30 (0.31)	84 (0.39)	0.80	0.72	0.47, 1.10
Brain cancer (191,192)	25 (0.26)	27 (0.12)	2.17	1.94	1.12, 3.34
Disease of circulatory system (390-459)	170 (1.76)	407 (1.88)	0.94	0.89	0.74, 1.06
Disease of respiratory system (460-519)	22 (0.23)	45 (0.21)	1.10	1.03	0.62, 1.72
Disease of digestive system (520-579)	24 (0.25)	46 (0.21)	1.17	1.10	0.67, 1.81
All external causes (E800-E989)	637 (6.60)	1460 (6.75)	0.98	1.01	0.92, 1.10
All accidents (E800-E929)	348 (3.61)	807 (3.73)	0.97	0.99	0.87, 1.12
Motor vehicle accident (E810-E929)	239 (2.48)	546 (2.52)	0.98	1.00	0.86, 1.17
Suicide (E950-E959)	174 (1.80)	386 (1.78)	1.01	1.05	0.88, 1.25

Note. ICD-9 = International Classification of Diseases, Ninth Revision; CI = 95% confidence interval. Exposure is to nerve gas as a result of demolition of weapons at Khamisiyah, Iraq. Exposure is based on the 2000 exposure model developed by the US Department of Defense.

[a]Crude death rates per 10 000 person-years at risk.

[b]Estimates of relative risk were derived from a proportional hazards multivariate model, with adjustment for age at entry to follow-up, race, sex, rank, and unit component.

US population, with adjustment for age, gender, race, and calendar year of death. The overall mortality for all 4 groups of veterans was less than half that expected as determined by the US population; the standardized mortality ratio for all exposed was 0.40 (95% CI=0.38, 0.42); the mortality ratio for those exposed 1 day was 0.40 (95% CI=0.38, 0.43); the mortality ratio for those exposed 2 or more days was 0.40 (95% CI=0.34, 0.47); and the mortality ratio for all unexposed veterans was 0.42 (95% CI= 0.40, 0.43). When we looked at cause-specific mortality, the only excess we found in cause-specific deaths among all groups of exposed veterans was brain cancer deaths. The largest excess of brain cancer deaths among exposed veterans was among those veterans exposed 2 or more days (SMR=2.13; 95% CI=0.78, 4.63). Those veterans exposed 1 day also had an excess of brain cancer deaths, but it was not statistically significant (SMR=1.05; 95% CI=0.63, 1.64). All unexposed veterans had a standardized mortality ratio for brain cancer deaths of 0.71 (95% CI=0.46, 1.04).

Exposure Misclassification

To assess potential effects of exposure misclassification, we conducted several sensitivity tests. In order for chemical exposure in Khamisiyah to no longer be associated with a statistically significant increased risk of brain cancer death, a minimum of 3 exposed brain cancer deaths would have to be reclassified as unexposed, yielding a relative risk of 1.64 (95% CI=0.95, 2.85). Changing the length of exposure of 1 brain cancer death from 2 or more days to 1 day also had little effect on the relative risk for 2 or more days of exposure (RR=2.71; 95% CI=1.03, 7.09). Even after we reclassified 3 brain cancer deaths from veterans exposed 2 or more days to veterans exposed only 1 day, the length of exposure remained significantly associated with the risk of brain cancer death.

Finally, assigning 7% of veterans with missing exposure data to first exposed and then unexposed groups and recalculating relative risks of brain cancer (RR=1.70; 95% CI=1.00, 2.90; and RR=1.97; 95% CI=1.16, 3.36, respectively) did not produce relative risks dissimilar to that reported in Table 2 (RR=1.94).

Smoke Exposure

Another potentially harmful exposure that could have affected a large number of Gulf War veterans was exposure to smoke from oil well fires.[12] To assess the extent of oil well smoke exposure, we added 3 different measures of smoke exposure data to the model cited in Table 2. The 3 different measures of smoke exposure were (1) the number of days of modeled exposure multiplied by the average concentration of total suspended particulate (TSP); (2) the number of days at TSP level of 0.260 mg/m^3 or more times the average concentration of TSP level for those days; (3) the presence or absence of TSP exposure of 0.260 mg/m^3 or greater. We limited these supplemental analyses to veterans with at least 1 day of modeled TSP exposure (n= 284 885). The 3 supplemental models yielded the following relative risk estimates of brain cancer deaths associated with Khamisiyah exposure: (1) relative risk was 2.25 (95% CI=1.12, 4.11), (2) relative risk was 2.30 (95% CI=1.26, 4.20), and (3) relative risk was 2.33 (95% CI=1.28, 4.25). None of these differ substantially from the original estimate of relative risk (RR=1.94; 95% CI=1.12, 3.34). To further assess the effects of exposure to smoke from oil well fires, we reran the models excluding the variable for Khamisiyah. None of the smoke exposure variables were associated with a statistically significant increased risk of brain cancer deaths.

Diagnostic Misclassification

In general, the accuracy of death certificates in determining cause of death is variable, especially regarding cancer-related deaths.[13,14] To determine which of the reported brain cancer deaths were most likely because of primary brain tumors, medical records were requested for all brain cancer deaths. Of the 55 brain cancer deaths, supplementary medical records were obtained for 42 veterans. A neurologist (R.T.J.; see Acknowledgments) who was blinded to

TABLE 3—Cause-Specific Mortality Risks Among US Army Gulf War Veterans Exposed at Khamisiyah, Iraq, in 1991 Stratified by Number of Days Exposed Compared With Unexposed Gulf War Veterans

Underlying Cause of Death *(ICD-9)*	1 Day Exposure (n = 86 167) No. (Rate[a])	≥2-Day Exposure (n = 14 320) No. (Rate[a])	All Nonexposed (n = 224 980) No. (Rate[a])	1-Day Exposure, RR[b] (95% CI)	≥2-Day Exposure, RR[b] (95% CI)
All causes	1020 (12.34)	159 (11.51)	2696 (12.47)	0.97 (0.90, 1.04)	0.96 (0.82, 1.13)
All diseases (001–799)	427 (5.17)	69 (5.00)	1093 (5.05)	0.95 (0.85, 1.06)	1.06 (0.83, 1.36)
Infectious and parasitic disease (001–139)	24 (0.29)	5 (0.36)	56 (0.26)	1.11 (0.69, 1.80)	1.49 (0.59, 3.74)
Malignant neoplasm (140–208)	156 (1.89)	28 (2.03)	391 (1.81)	0.94 (0.78, 1.13)	1.25 (0.85, 1.84)
Brain cancer (191, 192)	19 (0.23)	6 (0.43)	27 (0.12)	1.72 (0.95, 3.10)	3.26 (1.33, 7.96)
Disease of circulatory system (390–459)	147 (1.78)	23 (1.67)	407 (1.88)	0.88 (0.73, 1.07)	0.94 (0.61, 1.43)
Disease of respiratory system (469–519)	18 (0.22)	4 (0.29)	45 (0.21)	0.97 (0.56, 1.67)	1.58 (0.56, 4.42)
Disease of digestive system (520–579)	21 (0.25)	3 (0.22)	46 (0.21)	1.11 (0.66, 1.87)	1.02 (0.32, 3.31)
All external causes (E900–E989)	550 (6.65)	87 (6.30)	1460 (6.75)	1.01 (0.92, 1.12)	0.95 (0.77, 1.18)
All accidents (799–E929)	308 (3.73)	40 (2.90)	807 (3.73)	1.02 (0.89, 1.16)	0.79 (0.58, 1.09)
Motor vehicle accident (E810–E929)	213 (2.58)	26 (1.88)	546 (2.52)	1.04 (0.89, 1.22)	0.77 (0.52, 1.15)
Suicide (E950–E959)	142 (1.72)	32 (2.32)	386 (1.78)	1.00 (0.83, 1.21)	1.29 (0.90, 1.86)

Note. ICD-9 = International Classification of Diseases, Ninth Revision; RR = adjusted relative risk; CI = 95% confidence interval. Exposure is to nerve gas as a result of demolition of weapons at Khamisiyah, Iraq. Exposure is based on the 2000 exposure model developed by the US Department of Defense.

[a]Crude death rates per 10 000 person-years at risk.

[b]Estimates of relative risk were derived from a proportional hazards multivariate model, with adjustment for age at entry to follow-up, race, sex, rank, and unit component.

exposure status reviewed all available records to determine which deaths were because of primary gliomas. Of the original 55 brain cancer deaths, 47 were determined to be from primary brain tumors: 21 were from exposed subjects, 23 were from unexposed subjects, and 3 were from subjects with missing exposure data. Limiting brain cancer deaths to the 44 confirmed brain cancers with known exposure status, the risk of brain cancer death associated with chemical exposure in Khamisiyah was calculated with a proportional hazards model with adjustment for age at entry to follow-up, race, gender, rank, and unit component. Comparing exposed to unexposed veterans yielded an almost twofold statistically significant increased risk of brain cancer death associated with chemical exposure in Khamisiyah (RR = 1.88; 95% CI = 1.04, 3.41), virtually the same estimate as in Table 2. When we used only the 44 confirmed brain cancers, the relative risk estimate for those exposed 1 day was 1.66, and for those exposed 2 or more days, the RR estimate was 3.25.

Latency Analysis

The study's 10-year follow-up was divided into 3 follow-up periods of approximately equal length: original entry to follow-up to January 31, 1994 (follow-up 1); February 1, 1994, to July 31, 1997 (follow-up 2); and August 1, 1997, to December 31, 2000 (follow-up 3). For each follow-up period, an adjusted relative risk was calculated using the Cox proportional hazards model with adjustment for age, race, gender, unit component, and rank. The adjusted relative risks and number of exposed and unexposed brain cancer deaths for each follow-up period were as follows: in period 1, 6 exposed veterans and 7 unexposed veterans with brain cancer deaths—relative risk was 1.80 (95% CI = 0.60, 5.36); in period 2, 5 exposed veterans and 10 unexposed veterans with brain cancer deaths—relative risk was 0.99 (95% CI = 0.34, 2.91); and in period 3, 14 exposed veterans and 10 unexposed veterans with brain cancer deaths, relative risk was 3.03 (95% CI = 1.34, 6.82).

DISCUSSION

We compared the overall and cause-specific mortality of US Army Gulf War veterans potentially exposed to low-level chemical agents at Khamisiyah to that of US Army Gulf War veterans not exposed to chemical agents. When the mortality of all exposed veterans was compared with that of all unexposed veterans, with adjustment for covariates, there were no statistically significant differences between exposed and unexposed veterans except for an increased risk of brain cancer deaths among exposed veterans (RR = 1.94; 95% CI = 1.12, 3.34). Veterans exposed 2 or more days had a larger relative risk of brain cancer deaths (RR = 3.26; 95% CI = 1.33, 7.96) than veterans exposed only 1 day (RR = 1.72; 95% CI = 0.95, 3.10) when both were compared with unexposed veterans.

When we looked at the possibility of exposure misclassification, we found that 3 or more brain cancer deaths in exposed veterans would have to be reclassified as deaths in unexposed veterans to materially affect our results. Changing 3 of the 6 brain cancer deaths in exposed veterans from deaths in veterans exposed 2 or more days to deaths in veterans exposed 1 day did not alter the conclusion of the analysis of the length of exposure and risk of brain cancer death. Adding subjects with missing exposure data to either the exposed or unexposed cohort also did not materially change the results. Finally, adding data indicating exposure to smoke from oil well fires did not alter the original findings. Other potentially harmful exposures were present

in the Gulf, but any of these exposures should be nondifferential regarding exposure as determined by the 2000 exposure model. As neither sarin nor cyclosarin are known carcinogens, it is possible that the demolitions at Khamisiyah may have involved additional agents or chemicals that were related to the increased risk of brain cancer death. The lack of data on pre- or post-Khamisiyah environmental or occupational exposures is also a shortcoming. When we examined the possibility of diagnostic misclassification, we found that limiting analysis to the 44 confirmed gliomas did not materially change the results.

When we looked at typical risk factors for brain cancer, we found that a Poisson regression model for brain cancer found the same risk factors—increased age, male gender, higher social class (here military rank)—that have been found in other studies,[15] except that there were no differences by race. Because there were no female brain cancer deaths, separate analyses could not be done by gender; however, Cox models such as those used in Table 2 were run separately for Whites and non-Whites. Although the risk of brain cancer deaths associated with Khamisiyah was higher among non-Whites than Whites (RR=3.14 vs RR=1.59, respectively), the confidence intervals overlapped. Reported environmental and occupational risk factors for brain cancers are few and are believed to account for only a small proportion of all brain cancer deaths. Ionizing radiation is one such factor.[15] Among the occupational groups reported to be at increased risk for adult brain tumors are petrochemical workers,[16] electrical workers and those exposed to electromagnetic waves,[17,18] and those exposed to agrochemicals.[19]

Despite the apparent robustness of this study's finding of an association between brain cancer death and possible exposure to chemical warfare agents, a certain measure of caution is needed in its interpretation. First, until quite recently there has been little evidence suggesting that subacute exposure to chemical warfare agents could cause any health effects at all.[2] However, recent animal studies reported alterations in the brain that could lead to memory loss and cognitive dysfunction[20] and sarin-induced immunosuppression.[21]

The short latency period suggested by this study is contrary to the reported latency period of tumors. The brain tumors from this study would at most have a latency period of 10 years if they were related to some exposure at Khamisiyah. Research on brain cancers associated with occupational exposure, specifically exposure to radiofrequency fields from cell phones, report a latency period of 10 to 20 years.[22] The same latency period characterizes most other cancers. However, a recent study of brain tumors among a group of young military radar operators reported a latency period of less than 10 years.[23] Cancers such as leukemia and multiple myeloma have reported latency periods of 2 to 3.5 years between exposure and death.[24]

We found an approximately twofold excess of brain cancer deaths, 12 to 13 excess deaths in a population of 100 000 veterans, associated with possible exposure to chemical warfare agents. This finding was adjusted for the effects of age, race, gender, rank, and unit component and was robust to the potential effects of exposure and diagnostic misclassification, as well as latency; the addition of data on exposure to smoke from oil well fires also had no material effect on this result. Moreover, although the data were very sparse, risk increased monotonically with the number of days of possible exposure. Although considerable caution is warranted in the interpretation of this finding, we suggest that further follow-up of this and other possibly exposed military cohorts be undertaken. ■

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Contributors

T.A. Bullman conducted the analyses and prepared the article. W.F. Page originated the study, supervised its progress, and coordinated data retrieval. C.M. Mahan provided assistance with data analysis. H.K. Kang participated in the origination and design of the study and provided administrative and material support. All authors reviewed drafts of the study, contributed to critical revision of the article, and provided assistance in all other aspects of study.

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Human Participant Protection

This project was submitted for institutional review board review, and approval was obtained from both the Department of Veterans Affairs and the National Academy of Sciences.

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Health Effects in Army Gulf War Veterans Possibly Exposed to Chemical Munitions Destruction at Khamisiyah, Iraq: Part I. Morbidity Associated with Potential Exposure

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In March 1991, U.S. troops detonated the Khamisiyah, Iraq, ammunition depot, possibly releasing two chemical warfare agents, sarin and cyclosarin. The long-term health effects associated with possible exposure to these chemical warfare agents are unknown. This study was undertaken to investigate whether possible exposure was associated with morbidity among Army Gulf War veterans using morbidity data for 5,555 Army veterans who were deployed to the Gulf region. Responses to 86 self-assessed health measures, as reported in the 1995 Department of Veterans Affairs National Health Survey of Gulf War Era Veterans, were evaluated. We found little association between potential exposure and health, after adjustment for demographic variables, and conclude that potential exposure to sarin or cyclosarin at Khamisiyah does not seem to have adversely affected self-perceived health status, as evidenced by a wide range of health measures.

Introduction

Immediately after the Gulf War, demolition was carried out in March 1991 at the Khamisiyah ammunition depot in southeastern Iraq. Troops who were possibly exposed to chemical warfare agents were identified subsequently by environmental and climatological modeling, in conjunction with unit location data for the days of the demolition.[1] In this article, we compare the morbidity outcomes in the group of Army veterans possibly exposed to low levels of chemical warfare agents with those of a similar group of unexposed Army personnel. The morbidity data were collected as part of the Department of Veterans Affairs (VA) National Health Survey of Gulf War Era Veterans (NHS).[2] Two other articles examine deaths associated with possible exposure[3] and morbidity associated with notification of possible exposure.[4]

On March 4 and 10, 1991, combat engineer and explosive ordnance disposal units of the U.S. Army XVIII Corps (Airborne) destroyed two large caches of 122-mm rockets, one in a bunker and the other in a nearby pit, at the Khamisiyah ammunition supply point, ~350 km southeast of Baghdad, Iraq. In October 1991, March 1992, May 1992, and May 1998, representatives from the United Nations Special Commission inspected Khamisiyah and detected the existence of sarin and cyclosarin in both intact and damaged rockets in the bunker and pit.[1]

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Approximately contemporaneously, concerns increased about postwar morbidity among Gulf War veterans.[5-12] On June 21, 1996, the Department of Defense (DoD) released a statement confirming that U.S. soldiers had destroyed ammunition bunkers at Khamisiyah, Iraq, and that one of these bunkers contained chemical warfare agents.[13] Following this, the DoD made efforts to determine who was possibly exposed to chemical agents (see below) and also made efforts to notify veterans of possible exposure; the effects of these notification letters are the subject of another article.[4]

Toxicology of Nerve Agents Sarin and Cyclosarin

Sarin, an organophosphorus ester, is a highly toxic nerve agent. Exposure to acutely toxic concentrations can produce excessive bronchial, salivary, ocular, and intestinal secretions, as well as sweating, miosis, bronchospasm, bradycardia, muscle fasciculations, paralysis, convulsions, and death.[14] Minimal effects observed at low concentrations include miosis, chest tightness, rhinorrhea, and dyspnea.[14] There is limited evidence associating sarin exposure at a level sufficient to produce acute cholinergic signs with subsequent long-term health effects, such as fatigue, headache, blurred vision, post-traumatic stress disorder (PTSD), and abnormal test results of unknown clinical significance.[15] At doses too low to produce acute cholinergic effects, there is insufficient evidence to determine whether there is an association with subsequent long-term health effects, in part because of a lack of well-controlled studies.[15] Cyclosarin is similar in composition to sarin, although less volatile. Its mechanism of action is similar to that of sarin, although less is known about its toxicity.[15] A recent study of self-reported, long-term (25–45 years), health effects among 1,339 veterans experimentally exposed to anticholinesterase agents (including 287 exposed to sarin) included neurological and psychological outcomes such as peripheral nerve disease, vestibular dysfunction, sleep disorders, anxiety, and depression. There were only two statistically significant differences, i.e., subjects exposed to anticholinesterase agents had fewer attention problems than subjects in one control group and greater sleep disturbance problems than subjects in another control group. In contrast, self-reported exposure to hazardous chemicals outside the experimental testing program was significantly associated with all primary study outcomes.[16]

Methods

Study Population

The cohort for this study was selected in collaboration with the Office of the Special Assistant for Gulf War Illnesses, the

Deployment Environmental Surveillance Program of the U.S. Army Center for Health Promotion and Preventive Medicine, and the VA Environmental Epidemiology Service. Eligibility for entry into the cohort was based on the veteran having served in the Gulf theater of operations. Individuals identified as having been within and outside the modeled potential hazard area were eligible for inclusion. The cohort was further defined by having participated in Phase I of the VA NHS, conducted in 1995–1997.[2]

The NHS was designed as a retrospective cohort study in which health factors of a population-based sample of 15,000 troops deployed into the Gulf area were compared with those of 15,000 troops serving in the military during the period of the Gulf War but not in the Gulf area. Phase I of the survey was performed in 1995–1996, before troop notification of possible chemical agent exposure at Khamisiyah, Iraq, by the DoD. A total of 11,441 military personnel, who represented four branches of service deployed to the Gulf region during the 1990–1991 Gulf War, responded to either Phase I, the postal printed questionnaire survey in 1995–1996, or Phase II, the telephone interview survey in 1996–1997. The subset of veterans who participated in the postal questionnaire survey and who served in the Army numbered 5,555.

Determining Possible Exposure

The risk factors associated with the demolition in the Khamisiyah pit in March 1991 are possible exposures to chemical warfare agents, including sarin and cyclosarin.[1] For completeness, we also examined the data using exposure defined with the "50-km model," an early exposure model that declared Gulf War veterans who were within a circle with a radius of 50 km, centered at Khamisiyah, Iraq, to have been possibly exposed.[1] The history of DoD's exposure determination efforts is given below in brief.

Determining the possible risk of chemical agent exposure to U.S. troops in the vicinity of Khamisiyah began as a joint effort by the Central Intelligence Agency and the DoD in late 1996. It quickly became apparent that the pit demolition posed a number of challenges requiring expertise in modeling the physical characteristics of open-air demolition, as well as environmental and meteorological conditions at the site. The DoD-Central Intelligence Agency team used interviews with troops who had been at the site and test demolitions and other experiments at the Dugway Proving Grounds and Edgewood Laboratories to reduce uncertainties associated with the physical and environmental conditions at the site. Because of relatively scarce meteorological data for Iraq, the team used state-of-the-art mesoscale meteorological models to simulate prevailing weather conditions over the region. Dispersion models were then used to predict the transport and spread of chemical warfare agents, based on these simulated meteorological conditions. To account for uncertainty, a conservative assumption was made to define the potential hazard area as the union of the hazard areas given by each of the various combinations of meteorological and dispersion models. The result was the generation of a potential hazard area that varied in size and shape from March 10 to March 13, 1991. From this, the team was able to determine which units of troops were presumed to have been within the potential hazard area over the course of the 4-day period. The result of this effort is known as the "1997 hazard area" (see Ref. 1 for additional details).

Several factors contributed to the development of a subsequent exposure model, the remodeling effort or the "2000 hazard area." Meteorological modeling methods were further refined. The assumed amount of nerve agent released was reduced, based on more-recent intelligence analyses. The toxicity effects of cyclosarin were added to those of sarin, which was used alone in the 1997 analysis. Atmospheric removal mechanisms, such as dry deposition and degradation, were also considered. Finally, and possibly of most importance, unit location information was significantly improved in the 2000 model. Both models considered a soldier to have been exposed if his or her unit was in the hazard area but in 1997 the unit was generally at the battalion level (~1,000 soldiers), whereas in 2000 the unit was generally at the company level (~200 soldiers). Therefore, on average, an individual's unit was located with greater precision in the 2000 hazard area. In this study, an individual is deemed presumed exposed if, during any of the four 24-hour periods from March 10 to March 13, 1991, his or her unit was at a location that was exposed to a level of chemical warfare agent higher that the general population limit, adjusted for short-term exposure.[1] The general population limit is defined as the limit below which any member of the general population could be exposed daily, for a lifetime, and not experience any related adverse health effects. The modeling process also provided data on the number of days (0 or 1 through 4) of potential exposure. Although this does not constitute a true measure of intensity of exposure, we used number of days of exposure in some of our analyses as a limited proxy for intensity of exposure. We adopt the terms "exposed" to mean possible exposure under the 2000 hazard area, "unexposed" to mean no exposure under the 2000 hazard area, and "missing exposure" to mean that there was no 2000 hazard area exposure status assigned to an individual, because of missing or incorrect information identifying the individual or his or her military unit.

Through use of the 2000 hazard area and location data for soldiers at the company level in the Gulf region, exposure determination was provided for the 351,121 deployed Army personnel by the Office of the Special Assistant for Gulf War Illnesses. Record linkage of this chemical exposure data with the file of respondents to Phase I of the VA NHS yielded a total of 5,555 Army Gulf War veterans, who were classified into one of three categories of exposure to chemical agents, mainly sarin or cyclosarin, as follows: exposed Army Gulf War veterans, n = 1,898; unexposed Army Gulf War veterans, n = 3,336; missing exposure Army Gulf War veterans, n = 321.

Health Outcomes

Health perception data, before notification, were derived for all 5,555 Army Gulf War veterans who responded during Phase I of the VA NHS. The outcomes of interest are the self-assessments that were reported on the postal questionnaire developed for the VA NHS. The self-administered questionnaire was used to obtain information on the presence of various medical conditions and symptoms, measures of functional impairment, limitation of activity, and health care utilization.

A self-report symptom inventory composed of 48 items that were representative of the symptom configuration commonly

TABLE I

PREVALENCE OF SELECTED SEVERE SYMPTOMS DURING THE PAST 12 MONTHS ACCORDING TO EXPOSURE STATUS FOR 5,555 ARMY GULF WAR VETERANS

Symptoms Grouped by Organ System	Prevalence (%) Exposed (n = 1,898)	Prevalence (%) Unexposed (n = 3,336)	Adjusted Risk Ratio (95% CI)[a]
General			
Headaches	22.8	21.6	1.03 (0.93–1.15)
Runny nose	22.2	20.7	1.05 (0.94–1.17)
General muscle aches/cramps	12.2	13.7	0.88 (0.76–1.02)
Excessive fatigue	18.4	17.6	1.03 (0.91–1.16)
Fatigue >24 hours after exertion	10.1	10.6	0.94 (0.79–1.11)
Sleep difficulty	17.3	17.7	0.98 (0.87–1.11)
Sleepiness during daytime	11.1	11.5	0.96 (0.82–1.13)
Awaken tired or worn out	16.1	18.0	0.90 (0.79–1.02)
Fever or chills	4.3	4.1	1.05 (0.80–1.37)
Sweating not attributable to exercise	7.1	6.0	1.19 (0.96–1.48)
Skin, hair, and nails			
Skin rash	14.5	14.8	0.98 (0.85–1.12)
Hair loss	6.3	5.9	1.06 (0.85–1.32)
Ears			
Hearing loss	8.8	8.6	1.04 (0.87–1.25)
Mouth and throat			
Mouth, teeth, or gum problems	13.8	13.1	1.05 (0.91–1.21)
Sore throat or hoarse voice	10.9	9.8	1.08 (0.92–1.28)
Trouble swallowing	4.2	4.1	1.01 (0.77–1.33)
Respiratory			
Wheezing	6.7	8.2	0.81 (0.66–1.00)
Coughing	8.9	8.9	1.00 (0.83–1.20)
Breathing or shortness of breath	9.9	10.1	0.97 (0.82–1.15)
Cardiac			
Irregular heartbeat	5.1	5.7	0.88 (0.69–1.12)
Gastrointestinal			
Nausea	5.8	5.0	1.14 (0.90–1.44)
Vomiting	3.4	2.7	1.28 (0.93–1.75)
Stomach or abdominal pain	11.7	10.8	1.06 (0.90–1.24)
Reflux, heartburn, or indigestion	13.6	14.5	0.94 (0.82–1.08)
Diarrhea	11.8	11.3	1.07 (0.91–1.25)
Constipation	3.6	4.0	0.87 (0.65–1.16)
Genitourinary/reproductive			
Frequent/painful urination	4.2	4.4	0.91 (0.70–1.19)
Painful sexual intercourse	2.7	2.2	1.16 (0.81–1.65)
Impotence or other sexual problems	3.9	4.7	0.85 (0.65–1.12)
Musculoskeletal			
Back pain/spasms	20.2	20.9	0.97 (0.87–1.08)
Joint aches or pain	20.4	22.0	0.93 (0.83–1.04)
Swelling in any joints	6.8	8.6	0.79 (0.65–0.97)
Hematological			
Bruise or bleed easily	3.1	3.0	1.00 (0.73–1.37)
Sensory/neurological			
Loss of balance/dizziness	5.9	5.8	1.00 (0.80–1.26)
Blurred vision	4.2	4.6	0.90 (0.69–1.18)
Speech difficulty	1.7	2.1	0.77 (0.51–1.16)
Sudden loss of strength	6.6	5.9	1.12 (0.90–1.39)
Concentration/memory problems	13.8	12.8	1.06 (0.92–1.23)
Numbness in hands/feet	11.6	12.1	0.95 (0.82–1.11)
Tremor/shaking	3.5	3.9	0.89 (0.67–1.20)
Psychiatric			
Anxious, irritable, or upset	19.1	19.1	0.99 (0.88–1.11)
Been depressed or blue	16.1	15.0	1.06 (0.93–1.21)
Immunological			
Sensitive to chemicals	7.1	7.3	0.94 (0.77–1.15)
Lymphatic			
Swollen glands	5.0	5.5	0.89 (0.70–1.14)
Other (symptom meets the criteria for more than one category)			
Tightness in chest	6.2	7.1	0.87 (0.70–1.08)
Swelling of feet/ankles	4.5	5.2	0.84 (0.65–1.08)
Wound slow to heal	3.5	3.3	1.03 (0.77–1.40)

[a] Adjusted risk ratios (and 95% confidence intervals [CIs]) from Cochran-Mantel-Haenszel analysis, with adjustment for age, gender, race, rank, marital status, and unit component.

observed among outpatients was used to assess the prevalence of somatic and psychological symptoms. Complete lists of symptoms (Table I), grouped according to organ system, and conditions (Table II) are presented.

Questionnaire items were used to evaluate limitation of activity, prevalence of chronic conditions, self-assessed health status, and use of medical services, including physician contacts related to illness (excluding routine visits for vaccinations and physical examinations) and hospitalizations overnight. The PTSD Checklist, which was part of the survey instrument, contained 17 questions concerning PTSD symptoms experienced in the past 1 month.[17] A cutoff score of ≥50 points was used to classify veterans as having PTSD.[18] Participants were classified regarding the presence of chronic fatigue syndrome (CFS). The case definition that had been coordinated by the Centers for Disease Control and Prevention in 1994[19] was modified in terms of the time period for duration of symptoms that was available on the NHS survey instrument. This modification was described and evaluated elsewhere and is termed CFS-like illness.[20] Questions on smoking history and alcohol use were included, as well as weight change in the past 6 months. All of these outcomes were fully described elsewhere for the entire cohort of 11,441 Gulf War respondents and 9,476 non-Gulf War respondents.[2]

Demographic Characteristics and Military Variables

Basic demographic data and military variables (date of birth, gender, marital status, race, branch, rank, military occupational specialty code, and unit component) were derived from Defense Manpower Data Center (DMDC) and VA records. Date of birth, gender, and marital status were also investigated with the survey instrument. Gender, a binary variable, was coded as male vs. female. Age at the time of the Gulf War (1991) was recoded from the DMDC database as a binary variable, i.e., <30 years vs. ≥30 years. Race/ethnicity was coded into three strata, i.e., (1) Caucasian, (2) African American, or (3) Hispanic, American Indian, Alaskan Native, Asian, Pacific Islander, any other, or missing. Marital status at the time of the Gulf War, from the DMDC file, was converted to a binary variable, i.e., single vs. ever married. Rank at the time of the Gulf War was coded as a binary variable, i.e., enlisted vs. officer or warrant officer. Unit component was coded into three strata, i.e., Army active, Army National Guard, or Army Reserve.

Statistical Methods

Analyses measured the association between presumed exposure to chemical agents and the various health outcomes described in the survey instrument. We used contingency table

TABLE II

PREVALENCE OF SELECTED SELF-REPORTED MEDICAL CONDITIONS DURING THE PAST 12 MONTHS ACCORDING TO EXPOSURE STATUS FOR 5,555 ARMY GULF WAR VETERANS

Conditions	Prevalence (%)		Adjusted Risk Ratio (95% CI)[a]
	Exposed (n = 1,898)	Unexposed (n = 3,336)	
Arthritis	29.4	29.0	1.02 (0.93–1.11)
Lumbago	19.9	20.1	0.98 (0.88–1.10)
Diseases of muscles or tendons	10.3	10.4	0.98 (0.83–1.15)
Skin cancer	3.3	2.6	1.30 (0.94–1.79)
Other cancer	1.0	1.4	0.67 (0.40–1.12)
Eczema or psoriasis	10.5	9.5	1.11 (0.93–1.31)
Other dermatitis	35.6	34.2	1.03 (0.95–1.11)
Diseases of the hair or scalp, hair loss	22.6	21.5	1.05 (0.94–1.16)
Cirrhosis of liver	0.7	0.4	2.07 (0.97–4.42)
Hepatitis	1.7	1.3	1.32 (0.84–2.06)
Other liver disease	2.0	1.7	1.11 (0.74–1.67)
Gastritis	32.7	31.3	1.04 (0.96–1.13)
Enteritis	9.8	8.0	1.19 (1.00–1.43)
Colitis	8.6	6.0	1.39 (1.14–1.70)
Frequent diarrhea	29.6	28.9	1.03 (0.95–1.13)
Diabetes mellitus	1.3	1.4	0.92 (0.57–1.48)
Other endocrine disorder	2.6	2.6	0.92 (0.65–1.30)
Repeated seizures	3.1	3.5	0.89 (0.66–1.22)
Recurrent headaches	44.5	43.8	1.01 (0.95–1.08)
Migraines	20.0	21.3	0.93 (0.83–1.04)
Neuralgia or neuritis	6.8	6.4	1.05 (0.85–1.30)
Any disease of genital organs	6.3	6.6	0.94 (0.76–1.17)
Heart disease	1.8	1.8	0.98 (0.64–1.48)
Hypertension	15.1	14.8	1.03 (0.90–1.18)
Stroke	0.5	0.6	0.89 (0.42–1.88)
Tachycardia	11.9	12.7	0.92 (0.79–1.07)
Sinusitis	48.8	47.8	1.01 (0.96–1.07)
Bronchitis	15.1	14.5	1.02 (0.89–1.16)
Asthma	6.6	5.8	1.10 (0.88–1.37)
Other lung condition	6.8	7.3	0.96 (0.78–1.18)
Bladder infection	7.1	6.8	0.98 (0.80–1.20)

[a] Adjusted risk ratios (and 95% confidence intervals [CIs]) from Cochran-Mantel-Haenszel analysis, with adjustment for age, gender, race, rank, marital status, and unit component.

TABLE III

PERCENTAGE DISTRIBUTION OF SELECTED DEMOGRAPHIC/MILITARY SERVICE CHARACTERISTICS AMONG 5,555 ARMY GULF WAR VETERANS ACCORDING TO POSSIBLE EXPOSURE TO CHEMICAL AGENTS

	Exposed[a] (n = 1,898)		Unexposed (n = 3,336)		Missing Exposure (n = 321)	
Characteristics	No.	%	No.	%	No.	%
Gender						
Male	1,425	75.1	2,631	78.9	252	78.5
Female	473	24.9	705	21.1	69	21.5
Age (years) (mean in 1991)	31.0		30.9		29.8	
Interquartile range (years)	24–37		24–37		24–34	
Race						
Caucasian	1,363	71.8	2,405	72.1	237	73.8
African American	375	19.8	716	21.5	64	19.9
Hispanic	96	5.1	137	4.1	10	3.1
Other[b]	61	3.2	72	2.2	9	2.8
Missing	3	0.2	6	0.2	1	0.3
Marital status						
Married	1,006	53.0	1,760	52.8	155	48.3
Single	774	40.8	1,380	41.4	148	46.1
Other	118	6.2	196	5.9	18	5.6
Rank						
Enlisted	1,623	85.5	2,926	87.7	276	86.0
Officer	241	12.7	351	10.5	44	13.7
Warrant	34	1.8	59	1.8	1	0.3
Unit component						
Active	491	25.9	954	28.6	81	25.2
National Guard	742	39.1	1,328	39.8	32	10.0
Reserve	665	35.0	1,054	31.6	208	64.8

[a] Total (n = 5,555) is composed of possibly exposed (n = 1,898) plus unexposed (presumed not in hazard area) (n = 3,336) plus missing exposure status (n = 321). Possibly exposed is based on the DoD revised 2000 hazard area.

[b] Race "other" includes American Indian, Alaskan Native, Asian, Pacific Islander, and any other.

analysis to examine differences with respect to demographic and military factors between exposed and unexposed Army Gulf War veterans. Unadjusted risk ratios (relative risk) were calculated directly from the raw table entries. Adjusted risk ratios included adjustments for age in 1991 (<30 years vs. ≥30 years), gender, race/ethnicity (Caucasian, African American, or all other, including Hispanic), marital status (single vs. all other), rank (enlisted vs. officer or warrant officer), and Army active duty vs. Army Reserve or National Guard service. These adjustment factors were chosen based on their potential association with health outcomes. We adjusted for these factors using a propensity score,[21] which, divided into quintiles, was used to stratify the Cochran-Mantel-Haenszel analyses. Statistical significance was ascertained by examining the coverage of 95% confidence intervals, and no adjustments were made for multiple comparisons. Computations were carried out with standard software.[22]

Imputation

To avoid losing observations because of missing demographic and military data in the DMDC data file, we extracted the corresponding items from the NHS Phase I postal questionnaire, when possible. For the few cases of missing values for the race variable for which this approach did not work (n = 10), we created a category of "missing" for the crude rates but pooled the 10 missing observations with the "other" race stratum for the calculation of adjusted risk ratios. No imputation was performed for item nonresponses regarding outcome variables.

Sensitivity Analyses

Because 5.7% of the Army Gulf War veterans had missing exposure data, a sensitivity analysis was conducted for the main outcomes, to assess the potential effect of these missing data. First, subjects in the unknown exposure group were added to the exposed group and compared with unexposed subjects. Second, subjects in the missing exposure group were added to the unexposed group and compared with exposed subjects.

Institutional Review Board Approval

This project was submitted for institutional review board review, and approval was obtained from both the Department of Veterans Affairs and the National Academy of Sciences.

Results

Characteristics of Exposed and Unexposed Army Gulf War Veterans

The demographic and military characteristics of the 5,555 Army Gulf War veterans are presented in Table III, categorized by the three levels of exposure to chemical agents. The exposed group had a greater proportion of female veterans than did the unexposed group (24.9% vs. 21.1%; $p < 0.01$) and differed by race, having fewer African American veterans (19.8% vs. 21.5%) and a greater proportion of "other" races (Hispanic, American Indian/Alaskan, or Asian/Pacific Islander) (8.3% vs. 6.3%) than the unexposed group (p = 0.013). Regarding unit component,

there was a greater proportion of reservists in the exposed group than in the unexposed group (35.0% vs. 31.6%; $p = 0.02$). There were no significant differences between the exposed and unexposed groups for the variables age, marital status, and rank.

Functional Impairment, Limitation of Work, and Medical Care Utilization Attributable to Illness

Approximately the same percentages of exposed Army Gulf War veterans and unexposed Army Gulf War veterans reported staying home all or part of a day because they did not feel well or as a result of illness or injury within the 2 weeks before the survey response (31.0% vs. 31.9%) (Table IV). The percentage distribution of number of days at home during the past 2 weeks is shown for both groups; there was no difference between these two distributions ($p = 0.15$). Similarly, 20.9% of exposed Gulf War veterans and 22.0% of unexposed Gulf War veterans reported that they were limited in employment or in the kind of work they could do around the house because of an impairment or health problem ($p = 0.36$). Less than 2% of the respondents did not answer either of these two questions. There was no difference between the exposed and unexposed groups in the number of clinic or doctor visits made during the past 12 months because of illness ($p = 0.62$). Approximately 6% of each group did not answer this question. Among the exposed veterans, 8.9% reported having been hospitalized overnight or longer for illness during the past 12 months, whereas the corresponding percentage among unexposed veterans was 9.2%. The percentage distributions of those hospitalized were not different between the two groups ($p = 0.88$). Item nonresponse rates for this question were 3.4% for the two groups.

Sensitivity Analyses

In Table V, we assumed that all Army Gulf War veterans with missing exposure data were actually exposed. We consequently found no statistically significant differences for functional impairment (bed days), limitation of employment, number of clinic or doctor visits, or number of hospitalizations. Conversely, when we assumed that the veterans with missing exposure data were actually unexposed (Table VI), we reached the same conclusion. Because these results are the same as those in Table IV, we excluded subjects with missing exposure data from the remainder of the analyses in Tables I, II, VII, VIII, and IX.

Perception of General Health

There was no difference in perception of general health status between exposed and unexposed veterans ($p = 0.72$; Table VII). The item nonresponse rate for this question was 14% for each group, which is higher than rates for other items in the survey because the physical placement of this item on the survey form meant that it was inadvertently skipped by participants.

TABLE IV

PERCENTAGE DISTRIBUTION OF FUNCTIONAL IMPAIRMENT, LIMITATION OF EMPLOYMENT, AND MEDICAL CARE UTILIZATION ATTRIBUTABLE TO ILLNESS AMONG 5,555 ARMY GULF WAR VETERANS ACCORDING TO EXPOSURE STATUS

	Exposed (n = 1,898)		Unexposed (n = 3,336)		Missing Exposure (n = 321)		
Conditions	No.	%	No.	%	No.	%	p^a
Functional impairment							
Bed days							
0	1,291	69.0	2,235	68.1	207	64.9	
1–2	352	18.8	602	18.4	71	22.3	
3–4	125	6.7	277	8.4	25	7.8	
≥5	102	5.5	167	5.1	16	5.0	
Not answered[b]	28		55		2		0.15
Limitation of employment							
No	1,479	79.1	2,568	78.0	258	81.1	
Yes	391	20.9	724	22.0	60	18.9	
Not answered[b]	28		44		3		0.36
Clinic visit during past 12 months							
None	760	42.9	1,398	44.3	133	44.3	
1–3	563	31.8	974	30.9	88	29.3	
4–6	238	13.4	437	13.8	38	12.7	
≥7	211	11.9	347	11.0	41	13.7	
Not answered[b]	126		180		21		0.62
Hospitalization during past 12 months							
None	1,669	91.1	2,926	90.8	286	93.2	
1	123	6.7	213	6.6	15	4.9	
2	28	1.5	59	1.8	5	1.6	
≥3	13	0.7	24	0.7	1	0.3	
Not answered[b]	65		114		14		0.88

[a] p, significance probability by χ^2 test of independence between exposure categories (known exposed vs. known unexposed) and health condition indicator.

[b] "Not answered" category is presented for interest but is not included in the denominator in calculation of percentages.

TABLE V

SENSITIVITY ANALYSIS WITH 321 VETERANS WITH MISSING EXPOSURE STATUS INCLUDED IN THE CATEGORY OF EXPOSED: PERCENTAGE DISTRIBUTION OF FUNCTIONAL IMPAIRMENT, LIMITATION OF EMPLOYMENT, AND MEDICAL CARE UTILIZATION ATTRIBUTABLE TO ILLNESS

Conditions	Exposed + Missing Exposure (n = 1,898 + 321)		Unexposed (n = 3,336)		p^a
	No.	%	No.	%	
Functional impairment					
Bed days					
0	1,498	68.4	2,235	68.1	
1–2	423	19.3	602	18.4	
3–4	150	6.9	277	8.4	
≥5	118	5.4	167	5.1	0.16
Not answered[b]	30		55		
Limitation of employment					
No	1,737	79.4	2,568	78.0	
Yes	451	20.6	724	22.0	0.22
Not answered[b]	31		44		
Clinic visit during past 12 months					
None	893	43.1	1,398	44.3	
1–3	651	31.4	974	30.9	
4–6	276	13.3	437	13.8	
≥7	252	12.2	347	11.0	0.52
Not answered[b]	147		180		
Hospitalization during past 12 months					
None	1,955	91.4	2,926	90.8	
1	138	6.4	213	6.6	
2	33	1.5	59	1.8	
≥3	14	0.7	24	0.7	
Not answered[b]	79		114		0.83

[a] p, significance probability by χ^2 test of independence between exposure category and health condition indicator.
[b] "Not answered" category is presented for interest but is not included in the denominator in calculation of percentages.

Prevalence of Severe Symptoms

On the survey instrument, the veteran was given the guideline for reporting a symptom experienced during the past year as "severe" if its presence was "sufficient to seek medical advice, take prescription drugs, lose work, or limit routine activities." The prevalences of severe symptoms for exposed and unexposed veterans are presented in Table I for 47 symptoms (one symptom pertained only to male veterans and was excluded). The adjusted risk ratios showed two statistically significant associations between exposure and self-reported severe symptoms, i.e., the rates of wheezing and of swelling in any joints were lower in the exposed group. Because one would expect 1 of 20 statistical tests performed at the $p = 0.05$ level to be statistically significant by chance, the finding of two significant risk ratios in 47 tests could well be attributable to chance alone.

Prevalence of Mild or Severe Symptoms

On the survey instrument, the veteran was given the guideline for reporting a symptom experienced during the past year as "mild" if its presence caused the veteran to be "just aware but not slowed down by symptoms, or sufficient to take nonprescription drugs to relieve the symptoms (aspirin, Tums, etc.)." The prevalence of either mild or severe symptom was computed for each of the 47 symptoms, and results were compared for exposed and unexposed veterans. The adjusted risk ratios were not materially different from those for severe symptoms.

Prevalence of Chronic Medical Conditions

The prevalences of 31 medical conditions during the past 12 months are shown in Table II for exposed and unexposed veterans. Of the 31 medical conditions in Table II, all except two showed the same rates in the exposed and unexposed groups; enteritis and colitis had significantly higher rates in the exposed group. Again, because one would expect 1 of 20 statistical tests performed at the $p = 0.05$ level to be statistically significant by chance, the finding of two significant risk ratios in 31 tests could well be attributable to chance alone.

In Table VIII, the prevalences of two symptom-based medical conditions, PTSD and CFS-like illness, are tabulated. There was no significant difference in the prevalence of either medical condition according to exposure status.

Alternative Measures of Exposure

Next, we examined the relationship between number of days of possible exposure to chemical agents from March 10 to 13, 1991, coded as 0, 1, or ≥2 days, and general health status, number of clinic or doctor visits, number of hospitalizations, PTSD, and CFS-like illness (Table IX). The χ^2 tests showed no relationships between the number of days exposed (coded as 0, 1, or ≥2) and any of the health status indices ($p > 0.50$). Finally, using an alternative definition of exposure based on the 50-km proximity, i.e., within the 50-km radius from Khamisiyah from March 10 to 13, 1991, we assessed the frequency distributions of the same health indices (Table X). The χ^2 tests showed no

TABLE VI

SENSITIVITY ANALYSIS WITH 321 VETERANS WITH MISSING EXPOSURE STATUS INCLUDED IN THE CATEGORY OF UNEXPOSED: PERCENTAGE DISTRIBUTION OF FUNCTIONAL IMPAIRMENT, LIMITATION OF EMPLOYMENT, AND MEDICAL CARE UTILIZATION ATTRIBUTABLE TO ILLNESS

	Exposed (n = 1,898)		Unexposed + Missing Exposure (n = 3,336 + 321)		
Conditions	No.	%	No.	%	p[a]
Functional impairment					
Bed days					
0	1,291	69.0	2,442	67.8	
1–2	352	18.8	673	18.7	
3–4	125	6.7	302	8.4	
≥5	102	5.5	183	5.1	0.16
Not answered[b]	28		57		
Limitation of employment					
No	1,479	79.1	2,826	78.3	
Yes	391	20.9	784	21.7	0.49
Not answered[b]	28		47		
Clinic visit during past 12 months					
None	760	42.9	1,531	44.3	
1–3	563	31.8	1,062	30.7	
4–6	238	13.4	475	13.7	
≥7	211	11.9	388	11.2	0.68
Not answered[b]	126		201		
Hospitalization during past 12 months					
None	1,669	91.1	3,712	91.0	
1	123	6.7	228	6.5	
2	28	1.5	64	1.8	
≥3	13	0.7	25	0.7	
Not answered[b]	65		128		0.88

[a] p, significance probability by χ^2 test of independence between exposure category and health condition indicator.
[b] "Not answered" category is presented for interest but is not included in the denominator in calculation of percentages.

TABLE VII

PERCENTAGE DISTRIBUTION OF PERCEPTION OF GENERAL HEALTH AS REPORTED BY VETERANS ACCORDING TO EXPOSURE TO NERVE AGENTS SARIN OR CYCLOSARIN

	Exposed (n = 1,898)		Unexposed (n = 3,336)	
General Health	No.	%	No.	%
Excellent	180	11.0	292	10.2
Very good	380	23.2	671	23.5
Good	582	35.6	1009	35.3
Fair	419	25.6	733	25.6
Poor	74	4.5	153	5.4
Not answered[a]	263		478	

Significance probability by χ^2 test of independence between exposure and general health status, $p = 0.72$, $\chi^2_4 = 2.08$.
[a] "Not answered" category is presented for interest but is not included in the denominator in calculation of percentages. The excess item nonresponse for this question is attributable to the position of the question on the survey instrument.

association between 50-km exposure defined and any of the health status indices ($p > 0.45$).

Discussion

A population-based sample of Army Gulf War veterans who participated in the NHS and who were presumed to have been exposed to chemical agents in Khamisiyah, Iraq, did not report higher rates of days spent in bed within the past 2 weeks, health limitation, or medical care utilization, as measured by outpatient office visits or inpatient hospitalizations within the past year, than did similar unexposed veterans. Similarly, the two groups perceived their health status to be the same when asked to classify themselves into one of five categories, ranging from excellent to very good, good, fair, or poor. After adjustment for possible differences in demographic/military characteristics, the subjects in the exposed and unexposed groups reported equal prevalences for 45 of 47 severe symptoms and for 29 of 31 medical conditions. We also note that, based on what is known about health effects following exposure to anticholinesterase agents, we would have expected differences in neurological and behavioral symptoms, which we did not observe.

TABLE VIII

PERCENTAGE OF SYMPTOM-BASED MEDICAL CONDITIONS ACCORDING TO EXPOSURE STATUS

	Prevalence (%)		
Medical Condition	Exposed (n = 1,898)	Unexposed (n = 3,336)	p^a
PTSD[b]	15.5	15.6	0.88
CFS-like illness	7.0	6.4	0.48

[a] p, significance probability by χ^2 test of independence between exposure and symptom-based medical condition.
[b] PTSD, ≥50 points by self-report on PTSD Checklist.

The accuracy of exposure measurement is always an issue in this kind of study. The fact that there have been three official exposure models to date shows that the science and technology have been evolving. Even so, there are some who doubt the accuracy of the process.[23] We were able to ascertain that the results we obtained were robust with respect to the choice of model, by performing analyses based on the most recent data, the 2000 hazard area, as well as the earliest data, the 50-km model. We also determined that our results were not likely to have been affected by missing exposure data; including veterans with missing exposure data in either the exposed group or the unexposed group had no noticeable effect on the study's results.

Regarding endpoints, there are known limitations to self-reporting. First, there is the issue of reporting bias. We note that the rates of self-reported illness we saw in this study are higher than those in the NHS.[2] This may be attributable to the fact our study population differed in some respects from the NHS. We

TABLE IX

DOSE-RESPONSE RELATIONSHIP BETWEEN NUMBER OF DAYS OF EXPOSURE AND GENERAL HEALTH, CLINIC VISITS, HOSPITALIZATIONS, PTSD, AND CFS-LIKE ILLNESS

	Rate (%) with Days of Exposure			
Health Status[a]	0 (n = 3,336)	1 (n = 1,740)	≥2 (n = 158)	p^b
General health				
Excellent	10.2	11.1	9.8	
Very good	23.5	22.7	29.4	
Good	35.3	36.0	31.5	
Fair	25.6	25.9	23.1	
Poor	5.4	4.4	6.3	0.54
Clinic visits				
None	44.3	42.4	48.6	
1–3	30.9	31.9	30.4	
4–6	13.8	13.5	12.2	
≥7	11.0	12.2	8.8	0.58
Hospitalizations				
None	90.8	91.1	90.7	
1	6.6	6.8	6.0	
2	1.8	1.4	2.6	
≥3	0.7	0.7	0.7	0.92
PTSD present	15.6	15.4	15.8	0.98
CFS present	6.4	7.0	6.3	0.73

[a] Missing outcomes were excluded from denominators when percentages were calculated.
[b] p, significance probability by χ^2 test of independence between number of days of exposure and health status indicator.

TABLE X

PERCENTAGE DISTRIBUTION OF GENERAL HEALTH, CLINIC VISITS, HOSPITALIZATIONS, PTSD, AND CFS-LIKE ILLNESS BY EXPOSURE STATUS ACCORDING TO THE MODEL OF 50-km RADIUS AROUND KHAMISIYAH

Health Status[a]	Exposed (n = 199)	Unexposed (n = 5,356)	p^b
General health			
Excellent	8.4	10.7	
Very good	25.3	23.5	
Good	36.1	35.1	
Fair	25.9	25.7	
Poor	4.2	5.1	0.87
Clinic visits			
None	44.9	43.8	
1–3	34.6	31.0	
4–6	11.4	13.7	
≥7	9.2	11.5	0.49
Hospitalizations			
None	91.6	91.0	
1	5.8	6.6	
2	2.1	1.7	
≥3	0.5	0.7	0.93
PTSD present	15.7	15.4	0.94
CFS present	8.0	6.7	0.45

See text for details on exposure.
[a] Missing outcomes were excluded from denominators when percentages were calculated.
[b] p, significance probability by χ^2 test of independence between exposure and health status indicator.

included only deployed Army Gulf War veterans, and our sample had slightly greater proportions of female veterans, non-Caucasian veterans, enlisted personnel, and National Guard or Reserve personnel. Nonetheless, the rates in our study resemble more closely those for deployed personnel than the lower rates seen for nondeployed personnel.[2] Second, there are limitations in the type of health outcomes that can be ascertained by questionnaire. We note that some of the long-term health effects seen among subjects with sarin exposure at levels high enough to cause acute cholinergic reactions[15] were manifested as abnormal test results (e.g., digital symbol test of psychomotor performance and encephalograms during sleep) of unknown clinical significance, which might not have been identified if they did not correlate strongly with specific questionnaire items. Therefore, because of the limitations imposed by self-report, the lack of differences in health between exposed and unexposed subjects should not be over-interpreted.

In summary, we conclude that self-reported health among deployed Army Gulf War veterans 5 years after potential exposure to low levels of chemical agents at Khamisiyah, Iraq, did not differ according to exposure status. These results were the same regardless of which of two exposure models were used and were not affected by missing exposure data.

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Health Effects in Army Gulf War Veterans Possibly Exposed to Chemical Munitions Destruction at Khamisiyah, Iraq: Part II. Morbidity Associated with Notification of Potential Exposure

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The purpose of this study was to examine the association of notification of potential exposure to chemical warfare agents in the 1991 Gulf War with subsequent self-reported morbidity. The study sample included 1,056 deployed Army Gulf War veterans who responded to the 1995 National Health Survey of Gulf War Era Veterans and who were resurveyed in 2000. One-half of the subjects had been notified of potential exposure to chemical warfare agents and one-half had not. Comparing notified and non-notified subjects, there were no statistically significant differences with respect to bed days, activity limitations, clinic visits, or hospital visits. Among 71 self-reported medical conditions and symptoms, there were 5 statistically significant differences, 4 of which were for lower rates of illness among notified subjects. Our findings contradict the prevailing notion that perceived exposure to chemical warfare agents should be considered an important cause of morbidity among Gulf War veterans.

Introduction

On March 4 and 10, 1991, combat engineer and explosive ordnance disposal units of the U.S. Army XVIII Corps (Airborne) destroyed two large caches of rockets at the Khamisiyah ammunition supply point, ~350 km southeast of Baghdad, Iraq. In a companion article,[1] we examined the association between possible exposure to the chemical warfare agents sarin and cyclosarin and self-reported morbidity. After the announcement of possible exposure to chemical munitions, the Department of Defense (DoD) undertook efforts not only to determine who was potentially exposed to nerve agents but also to notify military service personnel of their potential exposure.

In this article, we report on the association between notification of potential exposure and self-reported health using data from the National Health Survey of Gulf War Era Veterans. Our study of the effects of notification takes particular advantage of the fact that the National Health Survey of Gulf War Era Veterans collected initial data in 1995, before the commencement of notification activities. By readministering the identical health survey in 2000, we were thus able to examine postnotification self-reported health, having in hand the identical data on pre-notification self-reported health.

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Methods

Determining Notification of Potential Exposure

There were three outreach efforts by the DoD, of which the first two are relevant to this study. On the basis of available information and discussions with experts before extensive modeling efforts, the DoD sent letters and surveys in October 1996 to ~20,000 troops known to have been within a 50-km radius of Khamisiyah between March 1 and March 15, 1991. A 25-km zone was chosen as a conservative estimate of the distance at which the first noticeable effects of chemical agents would have been seen and was then doubled to a 50-km zone as an added safety measure, to ensure inclusion of all U.S. forces in transit through the Khamisiyah area. The letter informed individual service members that chemical munitions might have been destroyed at Khamisiyah. The response rate for this mailing was approximately 37% (n = 7,400 surveys returned). Although this effort did not specifically mention potential exposure to chemical warfare agents, we refer to it as the "50-km notification."[2]

On the basis of the results of the 1997 plume model,[2] the DoD subsequently mailed ~99,000 letters of notification, informing troops of their possible exposure to low levels of chemical warfare agents. At the same time, letters were sent to the individuals (~10,000) who had been contacted in the initial wave of notifications in October 1996, informing them that, in all likelihood, they had not been exposed to chemical warfare agents. We refer to this second notification effort as the "1997 plume notification." We counted as "notified" any veteran who received a 50-km notification letter or a 1997 plume notification letter.

The modeling efforts continued with a new plume, the "2000 plume model," which included several improvements (see Ref. [1] for details). On the basis of the results of this model, a third set of letters was sent in December 2000 to notify individuals of their potential exposure to chemical warfare agents. However, because our resurvey was completed before the third set of notification letters was sent, notification status in this study does not take into account the third set of letters. Because there were two notification efforts, separated in time, and the follow-up time from the last notification was relatively short, we did not examine the effect of notification on mortality rates.

Sample Composition

Samples of 15,000 Gulf War veterans and 15,000 non-Gulf War veterans were originally used to conduct the National

Health Survey of Gulf War Era Veterans. These samples were taken from the Defense Manpower Data Center cohorts described above, using a stratified sampling scheme. Both deployed and nondeployed samples were stratified with respect to gender and unit component (active duty, Reserve, or National Guard), with oversampling of women and non-active duty components. The original sample contained 20% women, 25% National Guard personnel, and 33% reservists; the corresponding proportions among all deployed personnel were 7%, 7%, and 10%, respectively. The response rate for the original health survey was 70%.

For the present study, a subsample of 1,200 respondents to the National Health Survey was selected. This random subsample was originally chosen to contain equal numbers of exposed and nonexposed Army veterans, as well as equal numbers of notified and non-notified Army veterans. However, the inadvertent inclusion of non-Army subjects meant that the final sample numbered only 1,056 subjects, of whom 756 (72%) provided responses. The response rate for notified subjects in the resurvey was 73% (438 of 600 subjects), and the response rate for non-notified subjects was 70% (318 of 456 subjects). This project was submitted for institutional review board review, and approval was obtained from both the Department of Veterans Affairs and the National Academy of Sciences.

Health Outcomes

The health outcomes were the same as those in the original health survey (see Ref. [3] for details). Briefly, the outcomes included the following: number of bed days, activity limitations attributable to health, number of doctor visits in the past 12 months, number of hospitalizations in the past 12 months, overall health status (e.g., good or fair), selected medical conditions, selected symptoms, birth defects (yes/no), life events scale results, and post-traumatic stress disorder scale results.

Statistical Methods

Because we used a multiple-stage survey design involving responses to the initial health survey and the resurvey, we chose not to weight the data for nonresponses. Simple prevalence rates for notified and non-notified subjects were compared with the χ^2 test, and the Cochran-Mantel-Haenszel test was used to compute adjusted risk ratios comparing notified subjects with non-notified subjects. We have not shown data for outcomes for which any table cell had <10 subjects, corresponding approximately to outcomes with a prevalence rate of <3%.

Risks ratios were adjusted for exposure status, initial health survey response, age in 1991 (<30 years versus ≥30 years), gender, race (Caucasian or Hispanic versus all other), marital status (single versus all other), rank (enlisted versus officer or warrant officer), and Army active duty versus Army Reserve or National Guard service. These adjustment factors were chosen based on their potential association with health outcomes. All except the first two factors were used to compute a propensity score,[4] which, divided into quintiles, was used to adjust for these factors in Cochran-Mantel-Haenszel analyses. We examined data for individual outcomes according to exposure and notification status and found no substantial interactions. Therefore, we subsequently analyzed only the effects of notification on health outcomes, adjusted for exposure status.

No adjustments for item nonresponse were made, although we compared respondents with nonrespondents to the second questionnaire, looking at demographic data and initial outcomes. An earlier analysis of the characteristics of respondents and nonrespondents to the initial health survey (not limited to Army personnel) showed nonrespondents to be, on average, younger, unmarried, non-Caucasian, and of enlisted rank; gender, branch of service, and unit component (active duty, National Guard, or Reserve) status were not associated with response status.[3] In addition, certain items, such as reported exposures while in the Gulf, should not have changed between the initial health survey and the resurvey. Data comparing initial survey and resurvey responses for these items thus provide information on potential reporting biases or lack of such biases.

Results

Table I shows selected characteristics of respondents and nonrespondents. In general, the distributions of characteristics among respondents and nonrespondents were similar. Respondents were, however, proportionally more female, Caucasian, and married, and there were proportionally more officers and soldiers with National Guard or Reserve status. There was a slightly larger proportion of notified subjects among respondents than among nonrespondents.

Table II addresses the issue of data quality by comparing items that should reasonably have been reported the same way in the initial health survey and in the resurvey. The items pertained to self-reported exposures while in the Gulf, and we tabulated the proportions of responses that were concordant

TABLE I

PERCENT DISTRIBUTION OF SELECTED CHARACTERISTICS OF RESPONDENTS (N = 756) AND NONRESPONDENTS (N = 300)

Characteristics	Respondents (n = 756)	Nonrespondents (n = 300)
Mean age in 1991 (years)	31.5	28.9
Gender (%)		
Male	72.2	83.3
Female	27.8	16.7
Race (%)		
Caucasian	75.5	69.7
African American	17.9	22.7
Other	6.6	7.6
Marital status (%)		
Married	54.4	48.3
Single	39.3	47.0
Other	6.3	4.6
Rank (%)		
Enlisted	84.8	89.3
Officer	13.1	10.3
Warrant Officer	2.1	0.3
Unit component (%)		
Active duty	27.4	39.7
National Guard	38.9	31.0
Reserve	33.7	29.3
Exposure notification status (%)		
Notified	57.9	54.0
Not notified	42.1	46.0

TABLE II

COMPARISON OF INITIAL AND RESURVEY RESPONSES FOR SELECTED ITEMS: PROPORTIONS OF RESPONSES THAT WERE CONCORDANT AND K STATISTICS, ACCORDING TO NOTIFICATION STATUS

	Notification Status			
	Non-Notified		Notified	
Exposure while in Gulf Region	Percent Agreement	κ (95% CI)	Percent Agreement	κ (95% CI)
Smoke from oil well fires	89.5	0.71 (0.62–0.81)	90.3	0.72 (0.64–0.80)
Petrochemical fumes	91.3	0.53 (0.38–0.69)	92.7	0.50 (0.36–0.65)
Burning trash/feces	89.2	0.68 (0.57–0.78)	90.0	0.58 (0.47–0.69)
Skin exposure to diesel/petrochemical fuel	75.3	0.49 (0.39–0.59)	80.1	0.57 (0.49–0.65)
CARC paint	83.2	0.54 (0.43–0.66)	83.5	0.64 (0.56–0.72)
Other paints, solvents, petrochemicals	74.5	0.40 (0.29–0.52)	76.4	0.50 (0.41–0.58)
Depleted uranium	90.5	0.54 (0.39–0.70)	86.1	0.55 (0.45–0.65)
Personal pesticides (e.g., flea collars)	73.0	0.44 (0.34–0.55)	76.1	0.49 (0.40–0.57)
Nerve gas	87.3	0.39 (0.23–0.56)	81.4	0.36 (0.24–0.47)
Mustard gas or blistering agent	90.8	−0.05 (−0.07 to −0.02)[a]	90.3	0.37 (0.22–0.53)
Wore chemical protective gear (other than for training) or heard chemical alarms	92.0	0.65 (0.52–0.78)	85.9	0.44 (0.32–0.56)
Involved in direct combat duty	84.4	0.55 (0.43–0.67)[a]	88.7	0.76 (0.69–0.82)
Witnessed any deaths	82.2	0.56 (0.45–0.66)	85.4	0.68 (0.61–0.75)
Suffered sexual assault	99.0	0.40 (−0.15 to 0.94)	99.5	0.50 (−0.10 to 1.10)
SCUD missile explosion within 1 mile	87.4	0.73 (0.65–0.81)	86.9	0.73 (0.67–0.80)

CARC, chemical agent-resistant compound; CI, confidence interval.

[a] Statistically significant difference between κ values for notified and not notified.

(survey and resurvey responses were the same), according to notification status. We noted that, with some exceptions, initial survey and resurvey responses agreed 85 to 95% of the time and κ values were ≥0.50, indicating reasonable agreement. In general, where there were differences in reporting, the rate of self-reported exposure was higher in the resurvey. More importantly, κ values for notified and non-notified subjects were the same for all except involvement in direct combat duty and exposure to mustard gas or blistering agent (with higher κ values for notified subjects).

Table III shows demographic data for non-notified and notified respondents. The non-notified subjects were significantly older, more likely to be female, more likely to be married, and more likely to have been in the National Guard or Reserves; there was no difference in race or rank between the non-notified and notified subjects.

Table IV shows data on the baseline prevalence rates from the initial health survey for bed days, activity limitations, clinic visits, hospitalization, and general health status, all unadjusted for covariates. Despite the demographic differences between non-notified and notified subjects, we noted no statistically significant differences between the non-notified and notified subjects in these crude rates. Tables V and VI display similar baseline data for medical conditions and symptoms, respectively. In Table VI, only excessive fatigue showed a statistically significant difference in baseline prevalence between non-notified and notified subjects, with a higher rate among non-notified subjects.

Tables VII, VIII, and IX contain estimates of the adjusted risk ratios for the association of various health outcomes in the resurvey with notification status. Risk ratios were adjusted for initial response, exposure status, and propensity score, including age, gender, race, marital status, rank, and type of service (active duty, National Guard, or Reserve). The Hosmer-Leme-

TABLE III

PERCENT DISTRIBUTION OF SELECTED CHARACTERISTICS OF NON-NOTIFIED AND NOTIFIED RESPONDENTS

	Distribution (%)	
Characteristics	Non-notified (n = 310)	Notified (n = 446)
Age in 1991		
<30 years	42.9[a]	57.6
≥30 years	57.1	42.4
Gender		
Male	74.2	79.4
Female	25.8	20.7
Race		
Caucasian or Hispanic	81.3	78.3
African American or other	18.8	21.7
Marital status		
Married	64.2	58.3
Single or other	35.8	41.8
Rank		
Enlisted	88.1[a]	82.5
Officer or Warrant Officer	11.9	17.5
Unit component		
Active duty	17.7[a]	34.1
National Guard	44.5	35.0
Reserve	37.7	30.9

[a] Statistically significant difference between notified and non-notified groups ($p < 0.05$).

show goodness-of-fit statistic for the propensity score analysis yielded a χ^2 value of 3.13 (8 *df*, $p = 0.93$), indicating a good fit. Table VII shows that there were no statistically significant dif-

TABLE IV

INITIAL HEALTH SURVEY: PERCENT DISTRIBUTION OF BED DAYS, LIMITATION OF ACTIVITY, AND MEDICAL CARE UTILIZATION ATTRIBUTABLE TO ILLNESS, ACCORDING TO NOTIFICATION STATUS

Condition	Distribution (%)		p^a
	Non-notified	Notified	
Bed days			
0	68.0	72.7	
1–2	19.6	18.5	
3–4	6.5	5.2	
≥5	5.9	3.6	
Not answered	—	—	0.36
Limitation of activity			
No	79.1	79.4	
Yes	20.9	20.6	
Not answered	—	—	0.93
Clinic visits			
0	38.1	43.8	
1–3	35.4	31.0	
4–6	12.5	12.4	
≥7	14.1	12.8	
Not answered	—	—	0.45
Hospitalizations			
0	93.0	91.4	
1	5.3	6.5	
2	0.7	1.6	
≥3	1.0	0.5	
Not answered	—	—	0.46
Health status			
Excellent	10.1	10.3	
Very good	21.6	20.6	
Good	38.1	38.7	
Fair	26.1	25.0	
Poor	4.1	5.4	
Not answered	—	—	0.95

Numbers of subjects in the "not answered" category are presented but are not included in the denominator in calculation of percentages.
[a] Probability value from χ^2 test.

TABLE V

INITIAL HEALTH SURVEY: PREVALENCE RATES OF SELECTED SELF-REPORTED MEDICAL CONDITIONS DURING THE PAST 12 MONTHS, ACCORDING TO NOTIFICATION STATUS

Medical Condition	Rate (%)		p^a
	Non-notified	Notified	
Arthritis	29.1	30.3	0.73
Lumbago	21.3	21.4	0.97
Disease of muscles/tendons	12.2	10.9	0.59
Skin cancer	3.6	4.5	0.52
Eczema or psoriasis	10.5	9.1	0.52
Dermatitis	36.1	35.3	0.83
Disease of hair/scalp, including hair loss	21.0	19.4	0.60
Gastritis	30.7	32.1	0.68
Enteritis	12.8	8.4	0.05
Colitis	8.9	6.8	0.30
Frequent diarrhea	27.4	29.9	0.45
Other endocrine diseases	4.5	2.3	0.08
Recurrent headaches	46.8	42.0	0.20
Migraines	19.0	20.3	0.66
Neuralgia or neuritis	6.2	7.5	0.50
Diseases of genital organs	8.1	6.3	0.34
Hypertension	16.2	17.4	0.68
Tachycardia	12.7	10.4	0.33
Sinus trouble	47.6	48.1	0.89
Bronchitis	14.6	12.4	0.39
Asthma	7.8	6.1	0.35
Other lung condition	7.2	6.1	0.53

Subjects in the "not answered" category are not included in the denominator in calculation of percentages. Medical conditions with <10 responding "yes" have been omitted.
[a] Probability value from χ^2 test.

ferences between non-notified and notified subjects with respect to the rates of bed days, activity limitations, clinic visits, or hospitalizations.

Table VIII shows that there were three statistically significant differences between notified and non-notified subjects in the prevalence of selected medical conditions, i.e., other cancer, recurrent headache, and neuralgia. Only recurrent headache was reported at a higher rate among notified subjects. An additional analysis of the numbers of medical conditions (on average, approximately four conditions per person) also showed no significant difference between notified and non-notified subjects, after adjustment for the factors listed above.

Table IX shows two statistically significant associations between notification status and self-reported severe symptoms, after adjustment for confounding factors, i.e., irregular heartbeat and bruise or bleed easily. In both cases, rates were lower among notified subjects. Aside from statistical significance, the range of estimated risk ratios was fairly narrow, and there were approximately as many risk ratios above 1.0 (six risk ratios) as below 1.0 (10 risk ratios). An additional analysis of the numbers of severe symptoms (on average, four or five per person) also showed no significant differences between notified and non-notified subjects, after adjustment for confounding factors. The data on post-traumatic stress disorder showed no statistically significant difference between notified and non-notified subjects (adjusted risk ratio, 1.05; 95% confidence interval, 0.604–1.826).

Discussion

The existence of baseline health survey data on a representative national sample of Gulf War veterans presented an opportunity to look at the possible effects of notification on health. The fact that the baseline health survey data were collected before notification and therefore were not subject to self-report biases is a clear advantage of this study. The requirement to conduct the health resurvey using the identical instrument, which allowed us to measure postnotification health status but also limited the scope of the resurvey, has advantages and disadvantages.

In general, response rates for the initial survey and the resurvey were quite similar, i.e., 70% (including telephone follow-up responses) in the initial health survey versus 72% in the mailed resurvey. Therefore, the total response rates for both health surveys were approximately one-half (i.e., 0.70 × 0.72). Compared with respondents, nonrespondents in the initial health survey[3] were more likely to be younger, non-Caucasian, not married, and of enlisted rank; this is nearly the same as the nonrespondent profile we observed for the resurvey (Table I).

TABLE VI

INITIAL HEALTH SURVEY: PREVALENCE RATES OF SELF-REPORTED SEVERE SYMPTOMS DURING THE PAST 1 YEAR, ACCORDING TO NOTIFICATION STATUS

Symptom	Rate (%) Non-notified	Notified	p^a
Any headaches	21.0	20.0	0.74
Hearing loss	8.5	9.7	0.56
Wheezing	10.1	6.6	0.08
Runny nose	23.4	22.7	0.83
Mouth, teeth, or gum problems	15.6	15.1	0.85
Sore throat or hoarse voice	12.0	10.4	0.48
Trouble swallowing	2.9	6.0	0.06
Coughing	10.7	9.2	0.50
Breathing or shortness of breath	11.1	7.2	0.07
Tightness in chest	5.2	5.6	0.79
Irregular heartbeat	6.2	4.7	0.38
Back pain/spasms	21.2	22.7	0.62
Swelling of feet/ankles	3.6	4.5	0.54
General muscle aches or cramps	12.1	13.3	0.62
Joint aches or pain	22.4	18.7	0.22
Numbness in hands/feet	12.4	12.4	0.99
Swelling in any joints	6.5	7.4	0.62
Bruise or bleed easily	3.6	3.4	0.88
Skin rash	16.2	12.6	0.16
Hair loss	6.5	6.3	0.91
Loss of balance/dizziness	4.2	5.7	0.38
Sudden loss of strength	6.9	6.1	0.67
Excessive fatigue	23.0	16.2	0.02
Fatigue >24 hours after exertion	10.8	8.8	0.36
Nausea	4.9	4.9	0.96
Vomiting	3.2	2.0	0.30
Stomach or abdominal pain	9.8	10.3	0.81
Reflux, heartburn, or indigestion	14.6	11.9	0.28
Diarrhea	8.4	9.0	0.80
Constipation	4.6	2.0	0.05
Frequent/painful urination	4.2	4.5	0.84
Impotence or other sexual problems	4.9	3.9	0.48
Fever or chills	4.2	4.7	0.75
Sweating not attributable to exercise	4.6	6.3	0.30
Sleep difficulty	18.7	13.9	0.08
Sleepiness during daytime	12.6	11.2	0.55
Awaken tired or worn out	17.4	14.6	0.29
Anxious, irritable, or upset	19.2	17.8	0.61
Been depressed or blue	14.6	15.1	0.86
Tremor/shaking	3.6	2.9	0.62
Wound slow to heal	3.9	3.2	0.58
Speech difficulty	2.6	1.4	0.21
Concentration/memory problems	15.4	13.5	0.49
Sensitive to chemicals	5.8	6.8	0.61

Subjects in the "not answered" category are not included in the denominator in calculation of percentages. Medical conditions with <10 responding "yes" have been omitted.

[a] Probability value from χ^2 test.

TABLE VII

RESURVEY: ADJUSTED RISK RATIO ESTIMATES FOR ASSOCIATION BETWEEN NOTIFICATION AND BED DAYS, ACTIVITY LIMITATION, AND MEDICAL CARE UTILIZATION

Outcome	Adjusted Risk Ratio[a]
Bed days (any versus none)	1.07 (0.87–1.31)
Activity limitations (yes/no)	1.11 (0.88–1.39)
Clinic visits (any versus none)	1.01 (0.82–1.24)
Hospital visits (any versus none)	0.91 (0.70–1.18)

[a] Adjusted for exposure status, initial health survey response, age, race, gender, marital status, rank, and type of duty (active duty, National Guard, or Reserve).

TABLE VIII

RESURVEY: UNADJUSTED AND ADJUSTED RISK RATIO ESTIMATES FOR ASSOCIATION BETWEEN NOTIFICATION AND SELF-REPORTED MEDICAL CONDITIONS IN THE PAST 12 MONTHS

Medical Condition	Unadjusted Risk Ratio	Adjusted Risk Ratio[a]
Arthritis	1.05	1.11 (0.89–1.38)
Lumbago	0.96	1.01 (0.79–1.29)
Diseases of muscles or tendons	0.81	0.89 (0.69–1.15)
Skin cancers	0.93	0.84 (0.55–1.28)
Other cancers	0.51	0.61 (0.38–0.97)
Eczema/psoriasis	0.80	0.71 (0.50–1.01)
Dermatitis or other skin trouble	0.99	1.01 (0.82–1.24)
Diseases of hair or scalp, including hair loss	1.06	1.20 (0.91–1.58)
Gastritis	1.02	1.06 (0.83–1.35)
Enteritis	0.89	0.95 (0.70–1.30)
Colitis	0.96	1.08 (0.76–1.55)
Frequent diarrhea	0.99	0.96 (0.75–1.24)
Diabetes mellitus	0.81	0.80 (0.49–1.30)
Other endocrine problems	0.89	1.08 (0.63–1.83)
Repeated seizures	0.77	0.70 (0.39–1.15)
Recurrent headaches	1.18	1.39 (1.12–1.73)
Migraines	1.07	1.12 (0.82–1.51)
Neuralgia or neuritis	0.67	0.60 (0.47–0.76)
Diseases of genital organs	1.08	1.16 (0.79–1.71)
Coronary disease	0.89	0.82 (0.54–1.25)
Hypertension	1.07	1.13 (0.82–1.54)
Tachycardia	0.93	1.00 (0.76–1.33)
Sinus trouble	0.97	1.03 (0.82–1.28)
Bronchitis	0.94	0.99 (0.78–1.26)
Asthma	0.86	0.96 (0.68–1.35)
Other lung condition	1.10	1.12 (0.78–1.61)

[a] Adjusted for exposure status, initial health survey response, age, race, gender, marital status, rank, and type of duty (active duty, National Guard, or Reserve).

A comparison of items concerning exposures while in the Gulf, for which reporting should have been identical in the initial survey and the resurvey, showed reasonable rates of agreement for most items, with only one statistically significant difference in κ levels between notified and non-notified subjects (Table II). It should be noted, however, that others found evidence of the unreliability of self-reports of similar factors.[5] Notified subjects were younger, more likely to be male, and less likely to be married than were non-notified subjects (Table III).

Tables IV to VI show that the notified and non-notified subjects had approximately the same health statuses, as measured in the initial health survey. Given the relatively large number of comparisons (71 health outcomes), it was not surprising to find one statistically significant difference, which can be attributed to the action of chance. Tables VII, VIII, and IX show that post-notification health was not adversely associated with notifica-

TABLE IX

RESURVEY: ADJUSTED RISK RATIO ESTIMATES FOR ASSOCIATION BETWEEN NOTIFICATION AND SELF-REPORTED SEVERE SYMPTOMS IN THE PAST 1 YEAR

Symptom	Unadjusted Risk Ratio	Adjusted Risk Ratio[a]
Any headaches	1.01	1.07 (0.83–1.38)
Blurred vision	0.87	0.79 (0.53–1.19)
Hearing loss	1.15	1.18 (0.82–1.69)
Wheezing	0.92	1.18 (0.81–1.71)
Runny or congested nose	0.89	0.93 (0.74–1.15)
Mouth, teeth, or gum problems	0.89	0.92 (0.71–1.19)
Sore throat or hoarse voice	0.86	0.94 (0.71–1.25)
Trouble swallowing	0.90	0.89 (0.56–1.43)
Swollen glands	0.88	0.82 (0.56–1.19)
Coughing	0.96	0.99 (0.69–1.41)
Breathing or shortness of breath	0.84	0.84 (0.61–1.17)
Tightness in chest	0.82	0.78 (0.57–1.08)
Irregular heartbeat	0.71	0.69 (0.51–0.93)
Back pain/spasms	0.90	0.90 (0.72–1.13)
Swelling of feet/ankles	1.13	1.16 (0.78–1.72)
General muscle aches or cramps	0.84	0.88 (0.69–1.12)
Joint aches or pain	0.90	0.99 (0.80–1.22)
Numbness or tingling in hands/feet	0.86	0.88 (0.70–1.11)
Swelling in any joints	1.11	1.01 (0.71–1.42)
Bruise or bleed easily	0.69	0.60 (0.41–0.88)
Skin rashes	1.02	1.11 (0.85–1.45)
Hair loss	1.06	1.03 (0.72–1.48)
Loss of balance/dizziness	0.90	0.78 (0.57–1.07)
Sudden loss of strength	0.96	1.10 (0.75–1.62)
Excessive fatigue	0.99	1.14 (0.89–1.46)
Fatigue >24 hours after exertion	0.91	1.00 (0.76–1.33)
Nausea	1.19	1.00 (0.58–1.71)
Stomach or abdominal pain	1.08	1.15 (0.80–1.64)
Reflux, heartburn, or indigestion	0.86	0.92 (0.69–1.23)
Diarrhea	1.01	1.08 (0.78–1.49)
Constipation	0.81	1.01 (0.61–1.67)
Painful urination	1.04	1.11 (0.73–1.69)
Impotence or other sexual problems	0.94	0.98 (0.72–1.34)
Fever or chills	1.14	1.19 (0.74–1.93)
Sweating not attributable to exercise	1.00	1.00 (0.70–1.43)
Sleep difficulty	0.88	0.97 (0.77–1.21)
Excessive daytime sleepiness	1.04	1.07 (0.82–1.41)
Awaken tired or worn out	0.82	0.86 (0.69–1.08)
Anxious, irritable, or upset	0.87	0.93 (0.75–1.14)
Been depressed or blue	0.83	0.83 (0.67–1.03)
Tremor/shaking	0.79	0.83 (0.57–1.20)
Concentration/memory problems	0.97	1.06 (0.81–1.39)
Sensitive to chemicals	1.21	1.34 (0.89–2.02)

[a] Adjusted for exposure status, initial health survey response, age, race, gender, marital status, rank, and type of duty (active duty, National Guard, or Reserve).

tion; there were five statistically significant associations, four of which were <1.00. Given the number of tests, such a set of findings could be attributed to chance. The one significantly elevated risk ratio among notified subjects was for recurring headaches as a medical condition ("Did you have any one of the following medical conditions: recurrent headaches?"); the corresponding association with symptoms of headache ("In the past year, have you had consistent or recurring problems with: any headaches?") was not statistically significant.

Although the health statuses of notified and non-notified, deployed, Army Gulf War veterans were very similar, as were the health statuses of potentially exposed and nonexposed, deployed, Army Gulf War veterans,[1] we must note that, in this study and our companion article, we studied only deployed Army personnel. It was important to limit our studies to deployed personnel because there are marked differences in self-reported health status between deployed and nondeployed Gulf War veterans,[3] but the design of our current study did not allow us to examine health differences associated with deployment.

It is not in our purview to speculate after the fact regarding what kind of notification letters should have been sent, if any. Nonetheless, it is clear that this exercise in risk communication was undertaken in circumstances that were far from optimal. First, exposure status was uncertain, as reflected in the fact that three notification efforts were undertaken sequentially, and some still doubt the accuracy of the exposure model.[6] In addition, there were no known health effects thought to have been associated with potential exposure. Although we might have expected that heightened perception of possible risk in the notified group would have led to higher self-reported rates of illness,[7] this was not the case. Perhaps this was attributable to the fact that media coverage had already increased awareness of the issue,[8] or perhaps it simply reflects a well-done job of risk communication. It is important to note that our findings contradict the prevailing notion that perceived exposure to chemical warfare agents should be considered an important cause of morbidity among Gulf War veterans.[9]

In summary, there were few adverse health effects associated with notification regarding potential exposure to nerve agents, a finding that contradicts the prevailing view. Our study was limited to deployed Army personnel, however, and these results may not be generalizable to other personnel. Those who may be planning future notification efforts may nonetheless take some comfort in the fact that there were few adverse effects seen in this study.

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