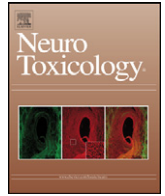




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## Spatial analysis of the etiology of amyotrophic lateral sclerosis among 1991 Gulf War veterans

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### ABSTRACT

**Background:** Veterans of the 1991 Gulf War have an increased risk of amyotrophic lateral sclerosis (ALS), but the etiology is unknown.

**Objectives:** This study sought to identify geographic areas with elevated risk for the later development of ALS among military personnel who served in the first Gulf War.

**Methods:** A unified geographic information system (GIS) was constructed to allow analysis of secondary data on troop movements in the 1991 Gulf War theatre in the Persian Gulf region including Iraq, northern Saudi Arabia, and Kuwait. We fit Bayesian Poisson regression models to adjust for potential risk factors, including one relatively discrete environmental exposure, and to identify areas associated with elevated risk of ALS.

**Results:** We found that service in particular locations of the Gulf was associated with an elevated risk for later developing ALS, both before and after adjustment for branch of service and potential of exposure to chemical warfare agents in and around Khamsiyah, Iraq.

**Conclusions:** Specific geographic locations of troop units within the 1991 Gulf War theatre are associated with an increased risk for the subsequent development of ALS among members of those units. The identified spatial locations represent the logical starting points in the search for potential etiologic factors of ALS among Gulf War veterans. Of note, for locations where the relative odds of subsequently developing ALS are among the highest, specific risk factors, whether environmental or occupationally related, have not been identified. The results of spatial models can be used to subsequently look for risk factors that follow the spatial pattern of elevated risk.

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### 1. Introduction

Although controversial, recent reports document an approximately twofold increase in the risk of amyotrophic lateral sclerosis (ALS) – a fatal neurological condition – among veterans of the 1991 Gulf War over the subsequent 10 years (Horner et al., 2003;

Coffman et al., 2005). This elevated risk was evident among deployed military personnel who were on active duty as well as in the Reserves and National Guard, and across all branches of service, with statistically significant elevations especially notable among those in the Air Force and Army. A second, independent study involving only Gulf War veterans under the age of 45 also found an elevated risk of ALS among this population (Haley, 2003). However, other earlier reports failed to identify an association between deployment and ALS among Gulf War veterans (Kang and Bullman, 1996, 2001; Smith et al., 2000; Sharief et al., 2002; Kelsall et al., 2005).

There are no reports on the occurrence of ALS among veterans of other conflicts, although the newly created Department of Veterans Affairs National ALS Registry may ultimately allow such investigation (Kasarskis et al., 2004; Allen et al., 2008). There is

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Abbreviations: ALS, amyotrophic lateral sclerosis; GIS, geographic information system; UIC, unit identification code; USACHPPM, US Army Center for Health Promotion And Preventive Medicine; NOAA, National Oceanic and Atmospheric Administration; PGVR, Persian Gulf Veterans Registry.

only a single report that suggests ALS may arise from environmental exposures associated with military service, *per se* (Weisskopf et al., 2005). A comprehensive review of the evidence on neurological disorders among veterans of the 1991 Gulf War reported no association between service in the Persian Gulf and the occurrence of neurological disorders, whether clinical syndrome or clinically defined disease, other than ALS (Rose and Brix, 2006). For diseases of unknown etiology such as sporadic ALS, the occurrence of a cluster of cases, especially among individuals who are expected to be at low risk (here, a majority of cases were under the age of 45 years) presents an opportunity to explore an environmental cause.

The relatively young age of the veterans who developed this condition is an infrequent occurrence, suggesting the possibility of an environmental or occupationally related cause, either alone or in interaction with a genetic predisposition or stress-mediated responses. In the 1-year period of military operations, deployed military personnel experienced numerous exposures to multiple, potentially neurotoxic agents (Spencer et al., 1998). If the array of possible candidate environmental exposures could be reduced, it may be possible to identify or at least focus inquiry on specific potential causative agent(s).

Geographic information systems (GIS) analysis is an analytic tool that has potential to achieve this objective through spatial characterization of military unit movements in the war zone. An example of this approach is demonstrated by Proctor et al. (2005) in an analysis of troop movement data and reported chronic multisymptom illness. By identifying those areas with elevated risk for the later development of particular health outcomes, more informed analysis of relevant risk factors can be performed. This paper directly considers the locations where troops were deployed in the theatre of war to determine whether there is any systematic pattern to the spatial locations of persons who eventually developed ALS. A GIS was established for the Southwest Asia area and then used as the basis for undertaking the spatial analysis. While relevant data were relatively limited, data on branch of service and potential of exposure to chemical warfare agents in and around Khamisiyah, Iraq, were available. These explanatory variables were incorporated into the analysis both separately and in combination.

## 2. Materials and methods

### 2.1. Study design

This is a secondary analysis of data from a nation-wide case ascertainment study of all new occurrences of ALS among veterans of the 1991 Gulf War from initial deployment in August 1990 through December 2001. This ascertainment period includes the additional year of surveillance for cases that was conducted after the original study ended. The Institutional Review Board at each performance site approved the study design and data collection protocols. The methodology of the original study is briefly summarized below; methodological details are available elsewhere (Horner et al., 2003).

### 2.2. Study population

For this investigation, the unit of analysis was the individual soldier, nested in a troop unit uniquely identified by a unit identification code (UIC). Fifty verified cases of ALS were identified among the military personnel who were deployed to Southwest Asia at any time during the period of 2 August 1990 through 31 July 1991. These cases were linked to their units based on their UIC as reported by the Defense Manpower Data Center.

Case identification occurred through nation-wide passive and active case ascertainment methods. Passive ascertainment involved a nationally publicized toll-free telephone number that individuals could call if they believed they were eligible for the study. Active case ascertainment involved screening extant Veteran's Administration (VA) and Department of Defense (DoD) inpatient, outpatient, and pharmacy databases using the International Classification of Diseases (9th Revision, Clinical Modification) diagnostic code for ALS (335.20) or use of riluzole, a drug indicated for the treatment of ALS. VA and DoD benefit files, and TriCare (a military health insurance plan) were also searched for individuals with a diagnosis of ALS. Potential participants were sent a letter describing the study and then telephoned to confirm their eligibility and determine their willingness to participate in the study. No financial incentives were offered for study participation.

Disease status was determined according to the most recent World Federation of Neurology El Escorial criteria for ALS (Brooks, 1994; Brooks et al., 1998). A case was defined broadly as any subject who met the criteria for clinically definite, probable, probable with supporting laboratory evidence, possible or suspected ALS (i.e., either lower or upper motor neuron signs and symptoms only). ALS was verified by medical record review for living subjects. If the subject was deceased, disease status was confirmed by either medical record review or, in the absence of medical records, by the underlying cause of death on the death certificate. Each subject's medical record was randomly assigned to two of five study neurologists who were specialists in ALS. Disagreements in the diagnosis (three occurrences) were resolved by consensus among the reviewing neurologists. In three additional cases, the reviewing neurologists agreed that further information was required, and the subject underwent a neurological examination to determine the diagnosis.

### 2.3. Military unit data

The US Army Center for Health Promotion and Preventive Medicine (USACHPPM) provided data on military troop unit movement, branch of service, and potential exposure to chemical warfare agents near Khamisiyah, Iraq. Military troop unit movement data, developed by the US Armed Services Center for Unit Records Research, tracked daily unit locations from the time of deployment into the Gulf War theatre through withdrawal from the region. The Defense Manpower Data Center's Persian Gulf Veterans Registry (PGVR) used these data to track individual service members' troop unit assignments during Operation Desert Storm, as well as their dates of entry and exit from the theatre. Among the 50 cases, 41 (82%) had records in the PGVR and could be linked to a specific troop unit.

The military troop unit data were originally provided in three tables, including:

- Location of all UICs, containing 705,246 records and described as having "distinct, daily locations of all troop units" in theatre including administrative UICs, which had person counts of 0.
- Locations of UICs that had at least one case.
- Locations of UICs with one or more cases but only for the days each case was actually in theatre.

All locations of administrative UICs were excluded from analysis. Because a UIC ( $n = 3327$ ) could be in multiple locations on any given day or its location data could be missing, a table (667,452 records) was created that contained at least one location for each UIC on each day the UIC was in theatre. In addition, each record includes a count of total ALS cases at that location for each

UIC (one UIC had two cases). When UICs were reported as being in more than one location on a given day, we assigned each corresponding areal unit one day of UIC time. Missing locations were imputed based on the previous day's location. If multiple locations were provided for a UIC on the day prior to a day with missing location information, multiple locations were imputed mirroring the spatial location/distribution of the UIC to the last known locations. These data were also used to calculate the total number of days in theatre.

#### 2.4. Environmental data

Regarding specific, known environmental exposures, USACHPPM provided a binary (1 = yes, 0 = no) variable that assessed the potential of exposure to chemical warfare agents in and around Khamisiyah, Iraq. Immediately following operation Desert Storm in March 1991, U.S. Army units conducted demolition operations around Khamisiyah, destroying numerous munitions bunkers, warehouses, and rockets. The United Nations Special Commission on Iraq later discovered that many of these rockets contained chemical warfare agents. There were, however, no reports of chemical warfare agent detections or reports of soldiers or civilians experiencing symptoms consistent with chemical warfare agent exposure. In January 2000, the DoD completed dispersion modeling of the demolition conducted at Khamisiyah to indicate potential hazard areas where some 99,000 veterans may have been exposed to low levels of nerve agent. The Khamisiyah exposure variable was provided in a separate table and was joined to the troop movement data using troop UICs.

#### 2.5. GIS analysis

After overlaying the troop movement data on the Gulf Region, we defined an area within which all troop movements occurred (Fig. 1). In Fig. 1a and b, the dots represent troop locations for UICs with and without service members who eventually developed ALS, respectively. Our primary goal in the analysis was to explore the importance of spatial location of the troops, as well as the impact of potential environmental exposure available through the admittedly limited data on chemical warfare agent exposure at Khamisiyah. This troop movement area was overlaid with an initial grid of 150 km square cells and subsequently subdivided into grids of 75 km and 37.5 km square cells. Within the initial 150 km square grid, those grid cells where at least one UIC spent at least one day were selected. In addition, all of these selected grid cells were buffered by cells from the 75 km grid. These two

selection criteria were used to define the study area. The statistical modeling used the 37.5 km square grid cells that were contained in the defined study area. Troop movements in the southeastern-most portion of this area were so sparse as to be non-sensible to include. Thus 27 troop locations associated with ships, and for which there were no ALS cases, were excluded from our analysis.

#### 2.6. Statistical approach

Poisson regression analysis was used to develop four models: (1) Model 1 models only spatial risk; (2) Model 2 adjusts for spatial risk and branch of service; (3) Model 3 adjusts for spatial risk and potential of exposure to chemical warfare agents in and around Khamisiyah; (4) Model 4 adjusts for spatial risk, branch of service, and potential exposure at Khamisiyah. Model 1, a purely spatial model, is designed to identify locations in the theatre with elevated risk, without controlling for any risk factors. Poisson regression models are especially helpful for analyzing disease count data and are readily amenable to this kind of spatial analysis.

Our model directly incorporates the spatial structure of the grid we overlay on the study region. This approach uses Bayesian disease mapping techniques to induce spatial dependence in the effects of the grid cells via specification of a conditionally autoregressive (CAR) prior distribution for the grid effects. In essence, this prior distribution compels neighboring grid cells estimates to “borrow strength” from one another, leading to improved accuracy and precision in estimating the grid effects. Indeed, our specification allows identification of the grid effects, which may not be possible in non-spatial approaches.

In addition, Bayesian models produce rich, flexible output. For example, we are able to directly estimate the probability that a grid cell is associated with elevated risk of ALS, a value that relies on both the estimate of elevated risk and the precision of the estimate. Such quantities are formally referred to as posterior probabilities, which are conditional probabilities that quantify our beliefs about parameters after the observed data is formally included in the model, i.e., after we update our prior beliefs in light of the observed data. Additional mathematical details about the modeling process can be obtained from the authors.

### 3. Results

Consistent with previous research, in both Models 2 and 4, Air Force personnel faced the greatest risk, followed by Army, Navy, and then Marine Corps personnel. In Model 4, estimated ALS incidence was 11.8 per 100,000 members of the Air Force, 7.1 per

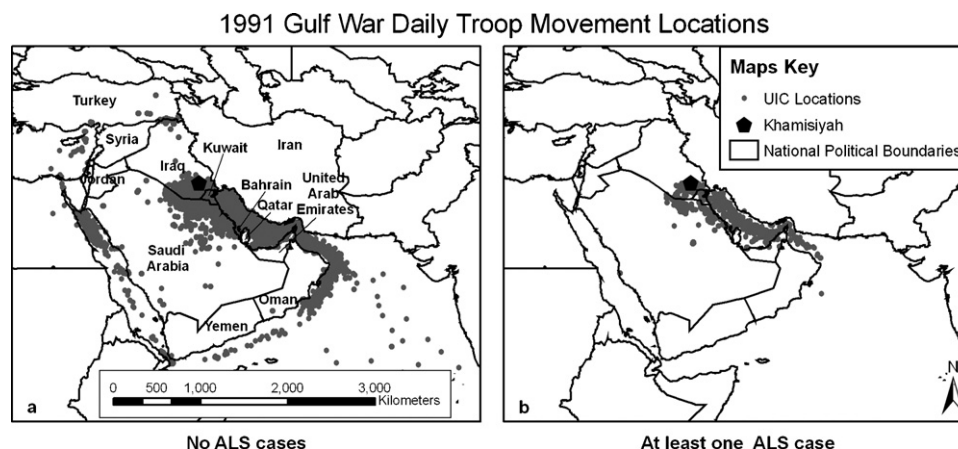


Fig. 1. UIC locations over duration of First Gulf War.

**Table 1**  
Estimated model parameters from Models 2 to 4, finest spatial scale

Model	Quantity	Estimate	95% credible interval
Model 2	Relative risk, Army (referent)	1.0	N/A
	Relative risk, Air Force	1.4	(0.6, 3.1)
	Relative risk, Marine Corps	0.2	(0.02, 0.7)
	Relative risk, Navy	0.3	(0.05, 0.9)
Model 3	Relative risk, Khamisiyah	1.9	(0.9, 3.9)
Model 4	Relative risk, Army (referent)	1.0	N/A
	Relative risk, Air Force	1.7	(0.6, 4.1)
	Relative risk, Marine Corps	0.2	(0.03, 0.9)
	Relative risk, Navy	0.3	(0.06, 1.1)
	Relative risk, Khamisiyah	1.7	(0.7, 3.7)

Note: Model 1 models only spatial risk, with no adjustment for branch of service or potential exposure at Khamisiyah, and therefore has no results to display in this table.

100,000 for the Army, 2.1 per 100,000 for the Navy, and 1.5 per 100,000 for the Marine Corps.

In both Models 3 and 4, there was some suggestion that potential exposure at Khamisiyah was associated with elevated risk of ALS. Although the 95% credible intervals (essentially a Bayesian version of a confidence interval) for the relative risk of potential exposure at Khamisiyah contained the null value 1, the estimated relative risk was about 1.7 in Model 4. Further, the posterior probability that this variable was associated with ALS was over 89%, providing some evidence in favor of such an association. Table 1 provides estimates and 95% credible intervals for Models 1 through 4 for key model parameters.

The estimated relative risk for each of the four models is summarized graphically in Fig. 2a-d. The median number of days in theatre for the UICs was 126 days (minimum of 1 day; maximum of 547 days). Thus, for each grid cell, we estimated the relative risk for an individual spending 126 days in that grid cell. In these maps, the darkest color tones represent the highest estimated relative risk. Note that we present these maps in grey-scale for ease of

### Estimated Relative Risk (126 Days)

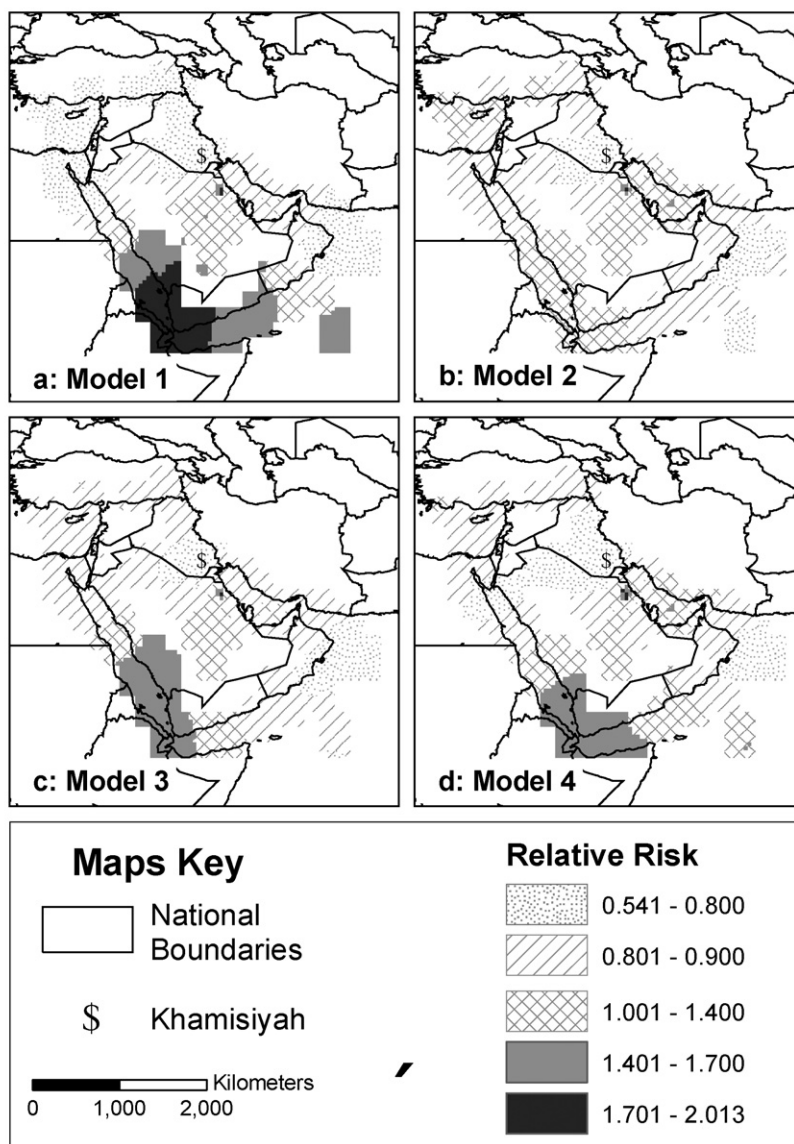


Fig. 2. Estimated relative risk for Models 1-4 based on individual spending 126 days in the grid cell.

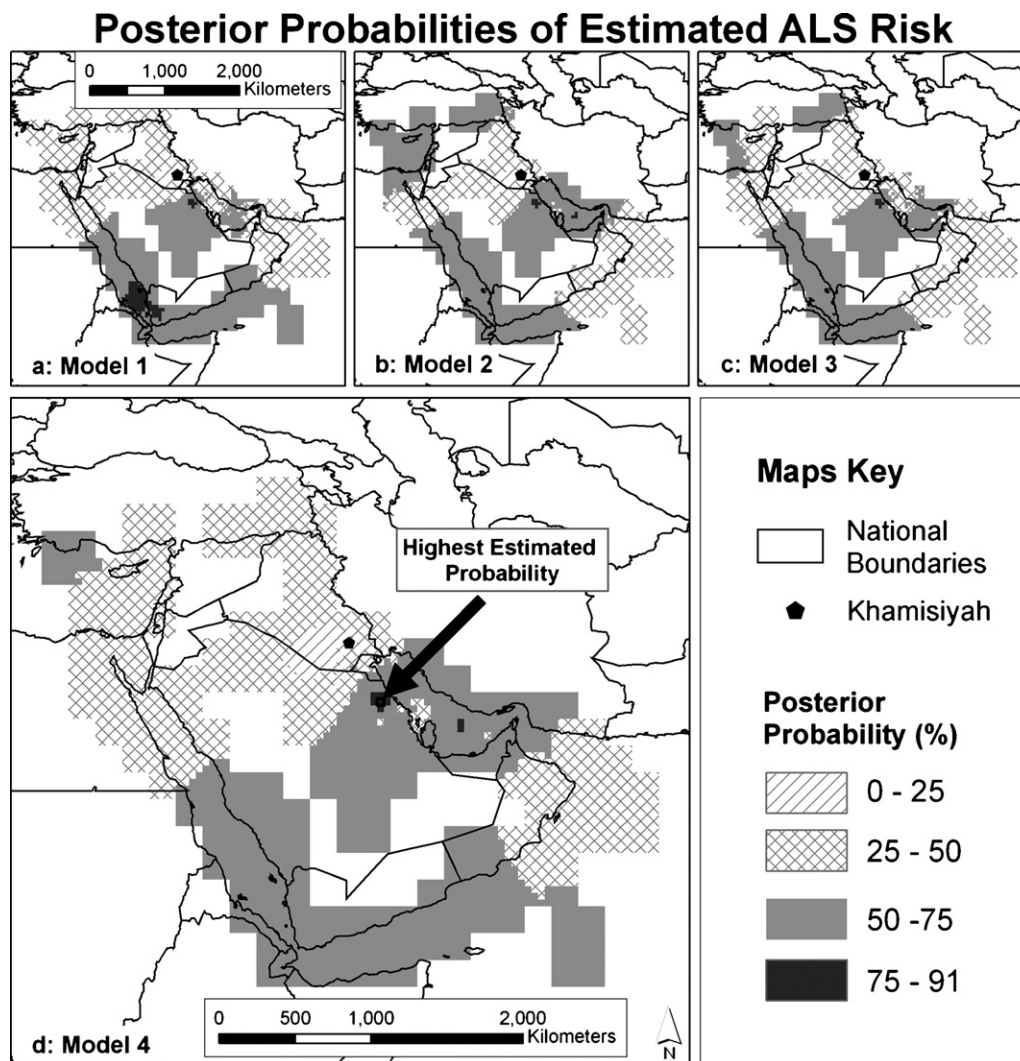


Fig. 3. Posterior probability of elevated ALS risk.

reproduction. (Color choropleths are available from the authors upon request.) Note especially the lightening of the dark area in the southwest quadrant after controlling for branch of service and/or potential exposure via Khamisiyah. In the figure, dark tones are associated with risks ranging from 1.4 to 2.0. It should be noted that the choice of 126 days is arbitrary. Any other number of days could be modeled, but would result in visually identical quintile-based choropleth maps where only the magnitudes on the legends would differ.

Fig. 3a–d shows the posterior probability of the elevated relative risk. In these maps, the darkest color tones denote greater than 75% posterior probability of elevated ALS risk. Similarly, the lightest color tones denote less than 25% posterior probability of elevated ALS risk. Again, note the shift in color tones associated with controlling for branch of service and/or exposure via Khamisiyah. Note also that the posterior probability of elevated ALS risk associated with any spatial location, even after controlling for branch of service and exposure via Khamisiyah, climbs as high as 91%. The posterior probabilities plotted in these maps are a direct result of the parameters estimated in the Poisson regression models and do not involve any need to choose a number of days spent in a particular grid cell.

We enlarge Fig. 3d in order to elucidate additional detail regarding the area identified as having the highest posterior

probability of elevated ALS risk. In Fig. 3d (which includes spatial, branch, and Khamisiyah model adjustments), within the darkest area, the grid cell (note arrow) has a posterior probability of over 90% of elevated risk of ALS. According to military data, a total of 230 UICs spent at least one day and up to 259 days in this area with UIC size ranging from 1 to 896 people. A soldier who spent 126 days in this specified area would have a 2.01 relative risk of developing ALS. Similar results obtained for the grid cells surrounding this area, thereby identifying this cluster of cells as an area with high probability of excess risk of ALS, with about a doubling of risk for troops who spent a typical amount of time in theatre, after adjusting for branch of service and potential exposure at Khamisiyah.

#### 4. Discussion and conclusions

In general, the etiology of ALS is unknown; only about 10% of cases have a familial history. For the 1991 Gulf War veterans who developed ALS, numerous potential etiologic agents are possible, including a genetic predisposition alone or in combination with environmental exposures or stress-related responses. However, among these Gulf War veterans who developed ALS, only three had a family history of the disease, which gives impetus to exploring environmental etiologies. This GIS analysis was conducted to

provide guidance as to specific locations where additional risk factors, environmental or otherwise, might be investigated.

We found some evidence of an association between particular locations and elevated risk for subsequently developing ALS. There is nothing about the location in and of itself that is risky. Rather, location serves as a proxy for latent variables that are not specifically incorporated into the analysis. Thus, the merit of the spatial model is that it becomes possible to subsequently look for risk factors that follow the spatial pattern of elevated risk. A more sophisticated spatio-temporal analysis focused on whether being in a particular location at a particular time is predictive would be an important extension of the current work. In looking for additional potential agents, the identified spatial “hot spots” may involve risk factors that can be evaluated further. An obvious risk factor candidate for inclusion would be exposure to oil well fire smoke. Some locations with high risk coincide with modeled plumes of oil well fire smoke (not included in our analyses), although whether the plumes and troop units were present *at the same time* has yet to be determined. This too would require sophisticated spatio-temporal modeling of troop locations within the plumes. In the future, spatio-temporal analyses may help determine if there is a link in time and space between risk factors and troop locations.

Beyond a time–space analysis, a more focused case–control study of exposures that emerge as potentially important may be warranted. Data on exposures were collected as part of the original study and may provide some of these targeted exposures. Others may be identified from an environmental assessment of potential agents in those geographic areas identified as “hot spots” in this report.

The different appearances of the maps based on the four models illustrate the importance of adjusting for putative risk factors. For example, comparing the estimated relative risks presented in Fig. 2a–d (which correspond to estimates from Models 1 through 4, respectively), the areas with highest and lowest estimated relative risk differs across maps. We also observe some differences in the maps of posterior probability of elevated relative risk of ALS (Fig. 3a–d) based on the four different models. Similarly, while generally consistent, the parameter estimates provided in Table 1 show some differences in the estimated effects of the non-spatial risk factors when in the presence of other risk factors. In short, the differences – both visual and numerical – that result when adjusting for putative risk factors underscore the importance of their inclusion, as well as the importance of identifying and including other potential risk factors.

We also found some evidence of an association between potential exposure to low levels of nerve agent from the destruction of the munitions and facilities at Khamisiyah and the subsequent occurrence of ALS among Gulf War veterans. However, the linkage of the chemical warfare agents at Khamisiyah to subsequent development of ALS must be viewed with considerable caution. For example, Khamisiyah exposures were represented as simple 0/1 binary variables indicating whether there had been potential exposure, and were at the UIC level. It is particularly important to note that with the available data, it is not possible to discern where in the chemical plume the members of the specific troop units were exposed and, hence, we cannot assign any probability or severity of exposure. And, it may be that other exposures occurred in the chemical plume area that actually account for the identified elevated risk. Also, the relative risk estimate lacks statistical robustness, with the credible intervals including the null value.

Still, even with the lack of more specific spatial or temporal information about the Khamisiyah exposure, the model is able to detect an increased risk even though the exposure occurred in

an area of overall low risk (see Fig. 2). Two related reports, though, indicate no association between possible exposure to the Khamisiyah plume and self-reported morbidity (Page, 2000; Page et al., 2005). Moreover, while a recent report found an elevated risk of mortality from brain cancers among those exposed to the Khamisiyah plume, there was no elevated risk for either all-cause mortality or broad categories of disease, although neurological disorders were not included in the analysis (Bullman et al., 2005). A recent Proctor et al. (2006) study does report a potential dose–response relationship between modeled exposure estimates at Khamisiyah and decreased central nervous system function on tasks dependent on psychomotor and visuospatial function. Additionally, linear trend analysis of magnetic resonance brain images found that veterans with higher modeled exposure to sarin/cyclosarin had increased right and left lateral ventricular volumes and decreased white matter volume indicating persistent neuro-anatomical changes (Heaton et al., 2007). These recent additions to the literature provide support of our findings indicating an association between exposures related to Khamisiyah and subsequent risk of developing ALS.

There are other limitations to our data that further constrain interpretation. For example, it may be useful to have a spatial–temporal summary measure of the troop movement data that measures the proportion of time that each UIC  $i$  spent in areal unit  $j$  compared to total time in theatre or, more simply, the total time that unit  $i$  spent in areal unit  $j$  (in the latter, coefficients from a logistic model would indicate time–location effects). Unfortunately, it is not possible to reliably construct these measures, as troops are often reported as being in more than one location on any given day. To provide a sense of the magnitude of the double counting, there are 738,077 reported location–day combinations, when the total number of days for all units is only 516,119; thus we were working with almost 150% of the actual data.

Another data limitation is that we used a dichotomous dependent variable that simply indicated whether an ALS case was present in a given military unit. We did not control for size of the unit. Of the 3784 UICs, 457 units do not have data on number of persons in unit. For units with the number of persons reported, the number ranges from a low of 1 (~45) to a high of 8399. However, given some of the data reliability issues already described and the generally low incidence of ALS, it did not seem sensible to alternatively construct a prevalence measure per unit.

Our purpose in conducting this GIS analysis was to determine whether there was any commonality to the spatial locations of troop units that included individuals who eventually developed ALS. One of the strengths of GIS analysis is that by including areal units in the analysis, it is possible to identify locations associated with a condition or disease in individuals who were in those areas. We found that those troops who subsequently developed ALS were in particular locations of service in the Gulf. Of note, for locations where the relative odds of subsequently developing ALS are among the highest, specific risk factors, whether environmental or occupationally related, have not been identified. A systematic search can be substantially enhanced by looking for risk factors that follow the spatial patterns elucidated in this analysis. This may yield insights into the excess risk of ALS experienced by Gulf War veterans.

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