RESEARCH ARTICLE

Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis survival

John D. Beard1,2*, Lawrence S. Engel1, David B. Richardson1, Marilie D. Gammon1, Coleen Baird3, David M. Umbach4, Kelli D. Allen5,6, Catherine L. Stanwyck5,7, Jean Keller8, Dale P. Sandler2, Silke Schmidt7, Freya Kamel2*

1 Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America, 2 Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, United States of America, 3 Environmental Medicine Program, US Army Public Health Command, Aberdeen Proving Ground, Maryland, United States of America, 4 Biostatistics and Computational Biology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, United States of America, 5 Durham VA Medical Center, Durham, North Carolina, United States of America, 6 Department of Medicine and Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America, 7 Department of Medicine, Duke University Medical Center, Durham, North Carolina, United States of America, 8 Westat, Inc., Durham, North Carolina, United States of America

* Current address: Department of Health Science, College of Life Sciences, Brigham Young University, Provo, Utah, United States of America

* kamel@niehs.nih.gov

Abstract

Background

Military veterans may have higher rates of amyotrophic lateral sclerosis (ALS) mortality than non-veterans. Few studies, with sparse exposure information and mixed results, have studied relationships between military-related factors and ALS survival. We evaluated associations between military-related factors and ALS survival among U.S. military veteran cases.

Methods

We followed 616 medical record-confirmed cases from enrollment (2005–2010) in the Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis study until death or July 25, 2013, whichever came first. We ascertained vital status information from several sources within the Department of Veterans Affairs. We obtained information regarding military service, deployments, and 39 related exposures via standardized telephone interviews. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals. We adjusted for potential confounding and missing covariate data biases via inverse probability weights. We also used inverse probability weights to adjust for potential selection bias among a case group that included a disproportionate number of long-term survivors at enrollment.
Results

We observed 446 deaths during 24,267 person-months of follow-up (median follow-up: 28 months). Survival was shorter for cases who served before 1950, were deployed to World War II, or mixed and applied burning agents, with HRs between 1.58 and 2.57. Longer survival was associated with exposure to: paint, solvents, or petrochemical substances; local food not provided by the Armed Forces; or burning agents or Agent Orange in the field with HRs between 0.56 and 0.73.

Conclusions

Although most military-related factors were not associated with survival, associations we observed with shorter survival are potentially important because of the large number of military veterans.

Introduction

Amyotrophic lateral sclerosis (ALS) is a debilitating neurodegenerative disease of motor neurons in the central nervous system [1]. Median survival after diagnosis is three years, but 4% of cases survive past 10 years [1]. Factors consistently associated with rapid progression or shorter survival include older diagnosis age [2–5], bulbar onset [2–6], clinical features (e.g., worse functional/disability status) [2, 3], shorter diagnostic delay [2, 5, 6], and definite diagnosis category [2]. Few studies, however, have considered non-clinical (e.g., occupational or environmental) prognostic factors for ALS survival, but these factors could help explain the extremely heterogeneous survival of ALS patients. In addition, identifying associations between non-clinical factors and ALS survival could help clinicians target interventions that may have the potential to lengthen survival, such as interdisciplinary palliative care [2], to patients at greatest risk of shorter survival.

Limited evidence suggests ALS rates may be higher among military veterans, particularly those deployed to the 1990–1991 Persian Gulf War (hereafter “Gulf War”) [7–10]. The few studies that examined associations between military-related factors and ALS survival or progression [5, 6, 11, 12] conflict and contain sparse exposure information. A study of the ALS Clinical Assessment, Research and Education database, a non-military database of North American patients [13], found no association between veteran status and survival [11], whereas a study in Massachusetts reported being a male veteran was associated with faster progression after one year of follow-up [6]. Deployment to the Gulf War was associated with shorter survival in one study [12], but not another [5]. The latter, based on the U.S. National Registry of Veterans with ALS (hereafter “Registry”) [14], also found shorter survival was associated with deployment to Vietnam, but not with cumulative military service, service branch, or deployment to Korea [5]. We evaluated associations between ALS survival and aspects of military service, deployments, and 39 related exposures using additional data on a subset of Registry cases enrolled in the Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis study (GENEVA) [15].

Funding: This work was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences (NIEHS; Z01 ES049005) (https://www.niehs.nih.gov/), grants from the NIEHS (R01 ES13244) and the ALS Association (ALSA 1230) (http://www.alsa.org/), and training grants from the NIEHS (T32 ES007018) and the Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health (T42OH00867302) (http://www.cdc.gov/niosh/). The National Registry of Veterans with ALS was supported by the U.S. Department of Veterans Affairs (CSP #500A) (http://www.va.gov/). JK is employed by Westat, Inc., a commercial company. Westat, Inc., provided support in the form of salary for an author (JK), but, along with the other funders, did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific role of this author (JK) is articulated in the “Author Contributions” section.

Competing interests: Jean Keller is employed by Westat, Inc. There are no patents, patent applications, or products in development or for market to declare. This does not alter the authors’ adherence to all the PLOS ONE policies on sharing data and materials, as detailed online in the guide for authors. The other authors declare they have no competing interests.
Materials and methods

Study population and outcome assessment

GENEVA is a case-control study of veterans, conducted from 2005–2010, that includes ALS cases from the Registry [14] and controls identified via U.S. Department of Veterans Affairs (VA) databases [15]. Although participants did not have to have been deployed to war to enroll in GENEVA, they did have to have been members of the U.S. Army, Air Force, Navy, Marine Corps, Coast Guard, activated Reserves or National Guard at some point in time [16, 17]. We previously used data on GENEVA cases and controls to evaluate associations between military-related factors and ALS etiology [17]. The present analysis focused on ALS survival and included cases only.

Methods used to enroll cases first in the Registry, then in GENEVA, were published previously [14, 15]. Briefly, the VA started the Registry because of increased ALS rates among veterans who had been deployed to the Gulf War [14, 15, 18]. Recruitment of potential cases occurred from 2003 to 2007 (i.e., the year the original Gulf War ALS studies [9, 10] were published to when funding expired) and included searches of national VA databases for patients with International Classification of Diseases, 9th Revision [19], codes of the form 335.2X (motor neuron diseases) and publicizing the Registry [14]. In total, there were 7,116 potential cases identified, 4,626 who completed a telephone screening [16], and 2,600 who reported a past diagnosis [14]. Of these, there were 2,400 who consented to join, 2,265 who allowed their medical records to be reviewed by ALS specialist neurologists, and 2,122 who had a diagnosis of ALS or another motor neuron disease confirmed using the Revised El Escorial Criteria [14, 20]. These 2,122 cases were followed until 2009 via standardized semi-annual telephone interviews [17].

The ascertainment of GENEVA cases from the Registry is shown in Fig 1. Of 1,856 ALS cases, there were 1,837 who gave permission to be re-contacted for further studies, 1,356 who consented to join the Registry DNA bank, and 847 who were able to be contacted regarding GENEVA enrollment. Of these, there were 726 who consented to join and 630 who enrolled, of which we included 616 in this analysis because they had information on diagnosis date and were not enrolled posthumously by proxy. These cases were comprised of patients with clinically definite, probable, possible, or suspected ALS.

The outcome we used was days from diagnosis date to death date or end of follow-up (July 25, 2013), with late entry at GENEVA enrollment date. Time since diagnosis was the most clinically meaningful time scale and allowing for late entry at enrollment date addressed potential immortal person-time bias, which occurs when follow-up time that occurs before the last event required to enter the study is counted as person-time at risk for death [21], from left truncation. Time to death is recommended over other ALS survival outcomes (e.g., time to use of ventilator or death), which are not uniformly defined or used across centers [22].

We extracted information on diagnosis date from medical records [16]. We obtained vital status information from the Austin Vital Status File, which contains information from several sources within the VA [23]. Using the National Death Index [24] as the gold standard, a validation study found the Austin Vital Status File was 98.3% sensitive and 99.8% specific (κ = 0.981) for identifying deaths among veterans [23]. Thus, it is likely we missed only a small proportion of deaths among GENEVA cases.

The Institutional Review Boards (IRBs) of the Durham VA Medical Center, Duke University Medical Center, and the National Institute of Environmental Health Sciences approved GENEVA; this ancillary study was approved by the IRB of the University of North Carolina at Chapel Hill. All participants provided written or oral informed consent before enrollment, which we tracked via Microsoft Access databases and documented by maintaining copies of
signed informed consent forms. We also mailed copies of informed consent forms to each participant. For the Registry, oral informed consent was sought and approved by the IRB of the Durham VA Medical Center when participants were unable to provide written informed consent due to the progression of their disease. For GENEVA, oral informed consent was sought

![Flow chart showing the ascertainment of GENEVA cases, United States of America, 2005–2010. Solid boxes or lines depict cases who progressed past each step shown. Small-dashed boxes or lines depict cases who did not progress past each step shown, but who were incorporated into the analysis indirectly via inverse probability weights (see Statistical Analyses and Section C in S1 File for more details). Among the 27 cases ineligible for GENEVA, reasons included dementia (n = 9), diagnosis change (n = 4), withdrawal from the Registry DNA bank (n = 3), or interview infeasibility (n = 11). Abbreviations: ALS, amyotrophic lateral sclerosis; GENEVA, Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis study; PLS, primary lateral sclerosis.](https://doi.org/10.1371/journal.pone.0185751.g001)
and approved by the IRBs of the Durham VA Medical Center and Duke University Medical Center for all ALS cases because the standardized telephone interview was deemed to involve no more than minimal risk of harm to the participants.

Exposure assessment

We used medical records as the source of information on clinical features and the Registry semi-annual telephone interviews [16] as the source of baseline (closest to GENEVA enrollment) ALS Functional Rating Scale-Revised (ALSFRS-R) score [17, 25]. Standardized telephone interviews for GENEVA [16] provided information on potential confounders and military service, deployments, and exposures that occurred before diagnosis date [15]. We had to conduct interviews via proxy for 27 (4%) cases. Interview procedures have been described in more detail elsewhere [15].

We collected information on military service—including longest service branch (i.e., the branch in which the veteran served the longest total time), number of branches, rank, total service time, and end of most recent service (Section A in S1 File)—and on deployments to World War II (WWII) and the Korean, Vietnam, and Gulf Wars (hereafter “four wars”) and operations in nine other locations—including ever deployment to any war/operation, war/operation of longest deployment (i.e., the war or operation to which the veteran was deployed for the longest total time), total time of all deployments, and end of most recent deployment [17] (Section A in S1 File). We also recorded information on ever deployment to any other country; ever receiving imminent danger pay, hardship duty, or combat zone tax exclusion benefits for deployment to 17 foreign countries and five sea regions (plus fill-in options); and total time deployed to those countries/sea regions [17] (Section A in S1 File).

To identify specific military exposures, we adapted questionnaires used in the Iowa Gulf War study [26] and the Millennium Cohort Study [27, 28] for use in GENEVA [15, 16]. We also added a few questions on exposures that were specific to one or more of the four wars (e.g., Agent Orange exposure during the Vietnam War) [17]. In total, we collected information on 39 specific military exposures, 32 of which we queried only in reference to exposure during deployment to the four wars [17], which included 16–228 cases depending on the war(s). For the seven non-war-specific exposures, we asked cases about ever exposure and, for some exposures, a quantification of exposure (e.g., number of pills) [17]. For 31 of 32 war-specific exposures, we collected information on whether cases had ever been exposed, days exposed (Not exposed, ≤ 5, 6–30, > 30), and whether they felt ill after exposure (Not exposed, No, Yes) [17]. For the other war-specific exposure, total vaccinations, we asked cases about number of shots received [17].

Statistical analyses

We used Cox proportional hazards regression models with time since diagnosis as the time scale to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between military-related factors and ALS survival. We checked the proportional hazards assumption by evaluating the statistical significance of interactions between each covariate and the natural logarithm of time since diagnosis [29].

We identified prognostic factors for ALS survival from previous literature to consider as potential confounders and used directed acyclic graphs [30] to identify minimally sufficient adjustment sets among these factors (Figure A and Section B in S1 File). For military service and deployment factors the minimally sufficient adjustment set was age and sex and for military exposures the minimally sufficient adjustment set was age, sex, and war/operation of
deployment. We did not include sex in our models due to small numbers of female cases (n = 13) and deaths (n = 10).

We calculated three types of stabilized inverse probability weights (hereafter “weights”) [31, 32], a type of propensity score, to adjust for potential bias from (1) confounding by age and war/operation of deployment (for military exposures), (2) missing data on ALSFRS-R score for 8% of Registry cases, and (3) selection arising from a case group that included a disproportionate number of long-term survivors at GENEVA enrollment [15] (Section C and Table A in S1 File). Although we calculated confounding weights for each exposure separately, we used the same missing-covariate-data and selection weights for every exposure. We assessed appropriateness of the weights using established criteria [31] (Section C in S1 File). We calculated overall stabilized weights by multiplying the three types of weights together [31, 33]. We then applied the overall stabilized weight to Cox proportional hazards regression models that contained the exposure of interest as the only explanatory variable (sampling weights are applied in the same way when analyzing data from complex survey sampling designs) [31, 33]. We used robust variance estimates to calculate 95% CIs for the HRs because using weights for analysis induces within-subject correlation [34].

Using weights for analysis creates a pseudo–population in which there is no bias from confounding, missing covariate data, or selection due to measured variables that are incorporated into the calculation of the weights [31, 32]. The weighted HRs and 95% CIs we calculated thus generalize to the 1,786 Registry cases who: had diagnoses of clinically definite, probable, possible, or suspected ALS; were not enrolled in the Registry posthumously by proxy; had diagnosis date available; and had no missing data on any covariates used to calculate the weights.

We used within-category medians as scores to assess linear exposure-response trends for categorized versions of continuous variables [35] and scaled corresponding HRs to one unit or interquartile range (IQR) increases in the original continuous variables. To assess linear trends for days exposed to each of 31 exposures experienced during deployment to the four wars, we used category midpoints, and 50% above the lower bound of the top category, as scores and scaled corresponding HRs to 20-day increases. We assessed linear trends for feeling ill after exposure to each of the same 31 exposures by using ordinal scores.

Our study is largely hypothesis-generating because most of the military-related factors we studied have not been evaluated in relation to ALS survival by previous studies. Therefore, we used the magnitude of associations (e.g., HRs greater than 1.25), the number of exposed ALS deaths (e.g., five or more), and, where appropriate, evidence of exposure-response trends rather than statistical significance to guide our choice of results to highlight in the text. However, we presented results for all military-related factors in the tables and S1 File for transparency and to stimulate further research.

Following the advice of several epidemiologists (e.g., [36–41]), we did not use conventional multiple comparisons adjustments, such as false discovery rate [42], because our study is not based on a random sample, does not include random exposure assignment, and assignment of exposures cannot be thought of as approximately random [43]. In addition, hierarchical regression models [44] were impractical for our study because of differing sample sizes available for the exposures and because it is not clear (1) how one would group the exposures, (2) whether the assumptions made to group the exposures would be valid [45], and (3) whether the groups would be meaningful chemically or biologically.

We performed several secondary analyses including separately analyzing war-specific exposures for veterans who were deployed to the Vietnam War (64% of those with war-specific data); the small number of veterans deployed to other wars precluded performing similar analyses for them. To reduce sample heterogeneity, we separately restricted to cases who: enrolled in GENEVA within two years of diagnosis (39%); had clinically definite or probable ALS
(75%); or never visited or resided in western Pacific regions with high endemic ALS [1] (84%). As an alternative way to control for confounding by age, we used age as the timescale, with late entry at GENEVA enrollment date. To control confounding by sex, we restricted to men (98%). We restricted to non-proxy interviews (96%) to mitigate potential bias from exposure misclassification. In addition, we recoded implausible values to missing for four exposures (anthrax vaccination, smallpox vaccination, nasopharyngeal radium, pyridostigmine bromide pills) that had distinct time periods of use. We identified correlations among the 39 military exposures by calculating Spearman correlation coefficients and then mutually-adjusted exposures that were more than weakly correlated (absolute value of coefficients $> 0.2$). Finally, we adjusted for potential confounding via standard regression methods, but did not weight for potential missing-covariate-data or selection bias. We conducted all analyses using SAS version 9.3 (SAS Institute Inc., Cary, NC, 2011).

**Results**

At the end of follow-up, 24,267 person-months had been observed since enrollment in GENEVA (Table 1). Median (IQR) follow-up was 28 (59) months and 446 (72%) cases had died (median [IQR] follow-up among the deceased was 17 [27] months). HRs increased with increasing age (Table 1). No other demographic characteristic was associated with survival.

After adjustment for age, HRs were higher among cases who had bulbar onset, but lower among those with longer diagnostic delays or higher baseline ALSFRS-R scores (Table 2). HRs decreased with increases in time from diagnosis to Registry enrollment, but increased with increases in time from Registry enrollment to GENEVA enrollment. Treatments associated with poor condition at baseline (e.g., use of ventilator) had elevated HRs.

In weighted analyses, HRs were elevated among cases who served $\leq$ 1 year in the military or before July 1950 (Table 3). Cases who were deployed to WWII or before July 1950 had higher HRs than those who were not deployed (Table 4). There was a significant inverse trend between end of most recent deployment and mortality (HR = 0.65; 95% CI: 0.48, 0.89), although category-specific associations were not monotonic.

Table 5 presents weighted results for ever experiencing specific exposures during service or deployment to the four wars; weighted results for analyses of exposure-response trends and feeling ill after exposure are in Tables B-C in S1 File. For exposures experienced any time during service, the HR for ever receiving anthrax vaccination was elevated but there was no exposure-response trend nor was there an association with feeling ill after exposure. Survival was not associated with ever taking pyridostigmine bromide pills, but HRs were elevated for taking them more recently, on more total days, and for taking more total pills per day and overall; however, all of these exposure-response metrics had fewer than five exposed deaths in some categories. For exposures experienced during deployment to the four wars, HRs were elevated for mixing and application of burning agents and there was a positive exposure-response trend. In contrast, HRs were decreased for field exposure to riot control substances or burning agents and the latter had an inverse exposure-response trend. HRs were elevated for high-intensity radar wave exposure, being within one mile of any explosion, and feeling ill after any explosion within one mile, but exposure-response trends were unapparent. HRs were lower for exposure to: paint, solvents, or petrochemical substances; local food not provided by the Armed Forces; hearing chemical alarms sounding; and Agent Orange, and the first three had inverse exposure-response trends. Cases who felt ill after local food exposure also had lower HRs than those who did not experience this exposure.

Sub-analyses restricted to veterans who were deployed to the Vietnam War generally showed similar results (Tables D-G in S1 File) as did restricting to reduce sample heterogeneity.
Table 1. Demographic characteristics of amyotrophic lateral sclerosis deaths and total cases in GENEVA, United States of America, 2005–2013.

| Characteristic                        | Deaths | Total | Crude | Adjusted |
|---------------------------------------|--------|-------|-------|----------|
|                                       |        |       | HR    | 95% CI   | HR    | 95% CI   |
| No. | PM  | No. | PM  |        |        |         |        |
| Total | 446 | 10,558 | 616 | 24,267 |        |         |        |
| Age (years)                           |        |       |       |          |        |         |        |
| ≤ 39 | 17 | 409 | 42 | 2,470 | 0.60 | 0.36, 1.02 |        |         |        |
| 40–49 | 35 | 1,150 | 68 | 3,853 | 0.74 | 0.50, 1.09 |        |         |        |
| 50–59 | 117 | 2,893 | 171 | 7,186 | 1.00 | Referent |        |         |        |
| 60–69 | 165 | 3,624 | 203 | 6,708 | 1.45 | 1.14, 1.84 |        |         |        |
| 70–79 | 100 | 2,264 | 119 | 3,767 | 1.45 | 1.11, 1.90 |        |         |        |
| > 79 | 12 | 219 | 13 | 283 | 1.98 | 1.09, 3.59 |        |         |        |
| Median (IQR) | 62 (14) | 60 (14) |       | 1.43 | 1.26, 1.63 |        |         |        |
| Sex |        |       |       |          |        |         |        |
| Male | 436 | 10,240 | 603 | 23,698 | 1.00 | Referent | 1.00 | Referent |        |
| Female | 10 | 318 | 13 | 569 | 1.00 | 0.53, 1.87 | 1.26 | 0.66, 2.39 |        |
| Race/Ethnicity |        |       |       |          |        |         |        |
| Non-Hispanic White | 413 | 9,491 | 561 | 21,419 | 1.00 | Referent | 1.00 | Referent |        |
| Other | 29 | 1,009 | 48 | 2,569 | 0.68 | 0.47, 1.00 | 0.74 | 0.51, 1.09 |        |
| Missing | 4 | 7 |       |       |        |         |        |        |
| Use of VA health care system |        |       |       |          |        |         |        |
| No | 254 | 5,920 | 361 | 14,502 | 1.00 | Referent | 1.00 | Referent |        |
| Yes | 192 | 4,639 | 254 | 9,686 | 1.04 | 0.86, 1.25 | 1.00 | 0.82, 1.21 |        |
| Missing | 0 | 1 |       |       |        |         |        |        |
| Ever applied for VA benefits of any type |        |       |       |          |        |         |        |
| No | 73 | 1,536 | 100 | 3,741 | 1.00 | Referent | 1.00 | Referent |        |
| Yes | 335 | 7,918 | 455 | 17,264 | 0.90 | 0.70, 1.16 | 0.92 | 0.71, 1.19 |        |
| Missing | 38 | 61 |       |       |        |         |        |        |
| Highest degree attained |        |       |       |          |        |         |        |
| Grade school (grades 1–8) | 17 | 496 | 20 | 753 | 1.22 | 0.74, 2.00 | 1.00 | 0.61, 1.66 |        |
| High school diploma or other | 191 | 4,455 | 266 | 10,474 | 1.00 | Referent | 1.00 | Referent |        |
| Technical or vocation school diploma or Associate degree | 81 | 1,604 | 114 | 4,207 | 0.95 | 0.73, 1.24 | 0.96 | 0.73, 1.25 |        |
| College or graduate school diploma | 145 | 3,692 | 199 | 8,152 | 0.98 | 0.79, 1.22 | 0.99 | 0.80, 1.24 |        |
| Doctorate | 12 | 310 | 17 | 681 | 0.88 | 0.49, 1.59 | 0.84 | 0.47, 1.52 |        |
| Cigarette smoking status |        |       |       |          |        |         |        |
| Never | 141 | 3,261 | 207 | 8,558 | 1.00 | Referent | 1.00 | Referent |        |
| Past | 232 | 5,531 | 305 | 11,380 | 1.13 | 0.92, 1.40 | 1.04 | 0.84, 1.29 |        |
| Current | 58 | 1,547 | 85 | 3,808 | 0.96 | 0.71, 1.31 | 1.02 | 0.75, 1.39 |        |
| Missing | 15 | 19 |       |       |        |         |        |        |

Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; GENEVA, Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis study; HR, hazard ratio; IQR, interquartile range; PM, person-months; VA, Department of Veterans Affairs.

* Fourteen ALS cases were excluded from this analysis because (1) they were missing data on diagnosis date (n = 7) or (2) they died before GENEVA enrollment (i.e., enrollment was completed by proxy after the case died; n = 7).

* Adjusted for age (modeled with indicator variables corresponding to 5-year groups).

* Person-months calculated for time on study (i.e., the difference between the GENEVA enrollment date and the death date or July 25, 2013).

* HRs and 95% CIs correspond to time since diagnosis accounting for late entry into the risk set at the GENEVA enrollment date.

* Scaled the HR to an IQR-unit increase in age among all cases.

https://doi.org/10.1371/journal.pone.0185751.t001
Table 2. Clinical characteristics of amyotrophic lateral sclerosis deaths and total cases\(^a\) in GENEVA, United States of America, 2005–2013.

| Characteristic                                      | Deaths                  | Total                  | Crude                   | Adjusted\(^h\)                  |
|-----------------------------------------------------|-------------------------|------------------------|-------------------------|----------------------------------|
|                                                     | No. | PM\(^c\) | No. | PM\(^c\) | HR\(^d\) | 95% CI\(^d\) | HR\(^d\) | 95% CI\(^d\) |
| Most recent ALS diagnosis category                  |     |          |     |          |          |            |          |            |
| Clinically definite                                 | 99  | 2,671    | 148 | 6,778    | 0.99    | 0.77, 1.26 | 1.04    | 0.81, 1.33 |
| Clinically probable                                 | 232 | 5,140    | 311 | 11,522   | 1.00    | Referent   | 1.00    | Referent   |
| Clinically possible                                 | 37  | 854      | 47  | 1,681    | 1.18    | 0.83, 1.67 | 1.22    | 0.86, 1.74 |
| Suspected (progressive bulbar palsy or progressive muscular atrophy) | 78  | 1,894    | 110 | 4,286    | 1.04    | 0.80, 1.35 | 0.98    | 0.76, 1.28 |
| Symptom onset site                                  |     |          |     |          |          |            |          |            |
| Bulbar                                              | 70  | 1,362    | 85  | 2,551    | 1.35    | 1.04, 1.75 | 1.23    | 0.94, 1.61 |
| Extremities                                         | 352 | 8,586    | 499 | 20,512   | 1.00    | Referent   | 1.00    | Referent   |
| Other\(^g\)                                         | 23  | 579      | 31  | 1,171    | 0.84    | 0.55, 1.29 | 0.96    | 0.63, 1.48 |
| Missing                                             | 1   | 1        |     |          |          |            |          |            |
| Time from symptom onset to diagnosis (months)        |     |          |     |          |          |            |          |            |
| ≤ 6                                                 | 90  | 2,299    | 116 | 4,483    | 0.85    | 0.65, 1.11 | 0.88    | 0.67, 1.15 |
| > 6–12                                             | 138 | 2,868    | 166 | 5,041    | 0.95    | 0.74, 1.21 | 0.86    | 0.67, 1.11 |
| > 12–18                                            | 73  | 1,434    | 104 | 3,869    | 0.74    | 0.56, 0.98 | 0.77    | 0.58, 1.03 |
| > 18–24                                            | 36  | 799      | 46  | 1,617    | 0.88    | 0.61, 1.28 | 0.85    | 0.59, 1.24 |
| > 24                                               | 104 | 2,940    | 172 | 8,426    | 0.56    | 0.43, 0.72 | 0.49    | 0.38, 0.64 |
| Missing                                             | 5   | 12       |     |          |          |            |          |            |
| Median (IQR)                                        | 11  | (15)     | 13  | (18)     | 0.82\(^f\) | 0.75, 0.91\(^g\) | 0.77\(^f\) | 0.70, 0.86\(^f\) |
| Time from diagnosis to enrollment in the Registry (months) |     |          |     |          |          |            |          |            |
| ≤ 12                                                | 185 | 3,372    | 216 | 5,699    | 1.00    | Referent   | 1.00    | Referent   |
| > 12–24                                            | 116 | 2,838    | 142 | 4,865    | 0.95    | 0.74, 1.21 | 0.86    | 0.67, 1.11 |
| > 24–36                                            | 47  | 1,091    | 75  | 3,347    | 0.76    | 0.53, 1.09 | 0.73    | 0.50, 1.05 |
| > 36–48                                            | 26  | 643      | 44  | 2,071    | 0.83    | 0.51, 1.32 | 0.76    | 0.47, 1.23 |
| > 48                                               | 72  | 2,614    | 139 | 8,284    | 0.73    | 0.44, 1.21 | 0.70    | 0.42, 1.17 |
| Median (IQR)                                        | 15  | (25)     | 19  | (32)     | 0.82\(^f\) | 0.66, 1.03\(^g\) | 0.82\(^f\) | 0.65, 1.02\(^f\) |
| Time from enrollment in the Registry to enrollment in the GENEVA study (months) |     |          |     |          |          |            |          |            |
| ≤ 6                                                | 140 | 2,795    | 178 | 5,634    | 0.99    | 0.78, 1.26 | 1.01    | 0.79, 1.30 |
| > 6–12                                             | 142 | 3,101    | 204 | 8,157    | 1.00    | Referent   | 1.00    | Referent   |
| > 12–18                                            | 72  | 1,951    | 95  | 3,896    | 1.36    | 1.02, 1.81 | 1.30    | 0.97, 1.74 |
| > 18–24                                            | 51  | 1,526    | 71  | 3,286    | 1.34    | 0.96, 1.86 | 1.36    | 0.97, 1.90 |
| > 24                                               | 41  | 1,186    | 68  | 3,294    | 1.31    | 0.90, 1.90 | 1.34    | 0.92, 1.95 |
| Median (IQR)                                        | 9   | (11)     | 9   | (11)     | 1.16\(^i\) | 1.01, 1.34\(^g\) | 1.18\(^i\) | 1.02, 1.37\(^i\) |
| Baseline\(^g\) ALSFRS-R score (possible range: 0–48)\(^h\) |     |          |     |          |          |            |          |            |
| ≤ 16                                               | 108 | 2,071    | 133 | 4,167    | 1.87    | 1.41, 2.47 | 2.09    | 1.57, 2.77 |
| > 16–23                                            | 94  | 1,815    | 116 | 3,674    | 1.50    | 1.13, 1.99 | 1.69    | 1.27, 2.25 |
| > 23–30                                            | 99  | 2,730    | 137 | 5,787    | 1.00    | Referent   | 1.00    | Referent   |
| > 30–35                                            | 77  | 1,792    | 111 | 4,466    | 0.88    | 0.65, 1.19 | 0.89    | 0.66, 1.21 |
| > 35                                               | 68  | 2,151    | 119 | 6,172    | 0.53    | 0.39, 0.73 | 0.56    | 0.41, 0.76 |
| Median (IQR)                                        | 26  | (16)     | 27  | (16)     | 0.54\(^i\) | 0.47, 0.62\(^g\) | 0.51\(^i\) | 0.44, 0.59\(^i\) |
| Currently using riluzole (baseline\(^g\))           |     |          |     |          |          |            |          |            |
| No                                                  | 207 | 5,107    | 298 | 12,448   | 1.00    | Referent   | 1.00    | Referent   |

(Continued)
Table 2. (Continued)

| Characteristic       | Deaths | Total | Crude | Adjusted<sup>b</sup> |
|----------------------|--------|-------|-------|----------------------|
|                      | No. PM<sup>c</sup> | No. PM<sup>c</sup> | HR<sup>d</sup> | 95% CI<sup>d</sup> | HR<sup>d</sup> | 95% CI<sup>d</sup> |
| Yes                  | 229    | 5,200 | 302   | 11,166              | 1.08              | 0.90, 1.31          | 1.14              | 0.94, 1.39          |
| Missing              | 10     | 16    |       |                      |                   |                   |                   |                   |

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; CI, confidence interval; GENEVA, Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis study; HR, hazard ratio; IQR, interquartile range; PM, person-months.

<sup>a</sup> Fourteen ALS cases were excluded from this analysis because (1) they were missing data on diagnosis date (n = 7) or (2) they died before GENEVA enrollment (i.e., enrollment was completed by proxy after the case died; n = 7).

<sup>b</sup> Adjusted for age (modeled with indicator variables corresponding to 5-year groups).

<sup>c</sup> Person-months calculated for time on study (i.e., the difference between the GENEVA enrollment date and the death date or July 25, 2013).

<sup>d</sup> HRs and 95% CIs correspond to time since diagnosis accounting for late entry into the risk set at the GENEVA enrollment date.

<sup>e</sup> Includes “all over” (deaths: n < 5; total: n < 5), “cramps/fasciculations” (deaths: n = 18; total: n = 26), and “loss of appetite” (deaths: n < 5; total: n < 5). Any numbers presented as “n < 5” were suppressed to preserve the confidentiality of study participants.

<sup>f</sup> Scaled the HR and 95% CI to an IQR-unit increase in time from symptom onset to diagnosis, time from diagnosis to enrollment in the Registry, time from enrollment in the Registry to enrollment in GENEVA, or baseline ALSFRS-R score among all cases.

<sup>g</sup> The ALSFRS-R score or use status of riluzole that was measured closest to the time of GENEVA enrollment (i.e., interview).

<sup>h</sup> Category boundaries were set at quintiles of the ALSFRS-R score among all cases.

https://doi.org/10.1371/journal.pone.0185751.t002

Table 3. Military service and amyotrophic lateral sclerosis survival in GENEVA<sup>o</sup>, United States of America, 2005–2013.

| Variable                                           | Deaths | Total | IP-weighted<sup>b</sup> |
|----------------------------------------------------|--------|-------|--------------------------|
|                                                   | No. PM<sup>e</sup> | No. PM<sup>e</sup> | HR<sup>d</sup> | 95% CI<sup>d</sup> |
| Military branch of longest service                 |        |       |                          |
| Air Force (including Army Air Force)               | 97     | 2,124 | 129 4,784                | 1.09              | 0.83, 1.44          |
| Army                                               | 182    | 4,403 | 249 9,775                | 1.00              | Referent            |
| Marines (including Merchant Marines)               | 36     | 638   | 55 2,175                 | 0.85              | 0.50, 1.43          |
| Navy                                                | 98     | 2,570 | 136 5,616                | 0.87              | 0.65, 1.16          |
| Other<sup>e</sup>                                   | 32     | 816   | 45 1,815                 | 0.76              | 0.51, 1.13          |
| Missing                                            | 1      | 2     |                          |
| Number of military branches of service             |        |       |                          |
| 1 (Median = 1)                                     | 411    | 9,774 | 565 22,300               | 1.00              | Referent            |
| > 1 (2)                                            | 35     | 785   | 51 1,967                 | 1.01              | 0.75, 1.38          |
| Officer or Warrant Officer                         |        |       |                          |
| No                                                  | 373    | 8,685 | 514 20,110               | 1.00              | Referent            |
| Yes                                                 | 72     | 1,858 | 100 4,060                | 0.96              | 0.72, 1.30          |
| Missing                                             | 1      | 2     |                          |
| Years of military service                          |        |       |                          |
| ≤ 1 (0.50)                                         | 13     | 241   | 15 400                   | 1.80              | 1.11, 2.90          |
| > 1–5 (2.92)                                        | 305    | 7,022 | 414 15,896               | 1.00              | Referent            |
| > 5–10 (7.92)                                       | 42     | 1,202 | 59 2,497                 | 0.88              | 0.59, 1.31          |
| > 10–15 (11.99)                                     | 14     | 436   | 26 1,398                 | 0.80              | 0.48, 1.33          |

(Continued)
| Variable            | Deaths | Total | IP-weighted |
|---------------------|--------|-------|-------------|
| No. PMc             | No. PMc| HRd  | 95% CI      |
| > 15–20 (18.92)     | 19     | 502   | 21          | 684       | 0.85 | 0.64, 1.11 |
| > 20 (24.31)        | 52     | 1,147 | 79          | 3,290     | 1.02 | 0.71, 1.47 |
| Missing             | 1      |       | 2           |           |      |            |
| Trend (IQR = 6.00)1  |         |       | 1.00        |           |      | 0.91, 1.10 |
| End of most recent period of military service (month/year)2 | | | | | |
| < 12/1946 (03/1946) | 26     | 593   | 32          | 1,073     | 1.58 | 0.96, 2.61 |
| 01/1947-06/1950 (02/1948) | 9  | 185  | 11          | 341       | 2.23 | 1.06, 4.70 |
| 07/1950-01/1955 (06/1953) | 48 | 1,332 | 56          | 2,003     | 1.04 | 0.71, 1.52 |
| 02/1955-02/1961 (12/1957) | 78 | 1,648 | 97          | 3,266     | 1.18 | 0.83, 1.70 |
| 03/1961-07/1964 (06/1963) | 34 | 849   | 43          | 1,603     | 1.04 | 0.66, 1.64 |
| 08/1964-04/1975 (07/1969) | 134 | 3,160 | 192         | 7,732     | 1.00 | Referent   |
| 05/1975-08/1980 (05/1978) | 26 | 606   | 42          | 1,903     | 0.92 | 0.54, 1.56 |
| 09/1980-07/1990 (03/1986) | 36 | 818   | 53          | 2,156     | 0.84 | 0.59, 1.21 |
| 08/1990-08/2001 (06/1994) | 44 | 1,177 | 71          | 3,299     | 0.99 | 0.65, 1.49 |
| > 08/2001 (10/2003) | 10     | 182   | 17          | 789       | 0.94 | 0.48, 1.83 |
| Missing             | 1      |       | 2           |           |      |            |
| Trend (20 years, 11.99 months)3 | | | | | | 0.98 | 0.81, 1.18 |

Abbreviation: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; CI, confidence interval; GENEVA, Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis study; HR, hazard ratio; IP, inverse probability; IQR, interquartile range; PM, person-months; VA, Department of Veterans Affairs.

1 Fourteen ALS cases were excluded from this analysis because (1) they were missing data on diagnosis date (n = 7) or (2) they died before GENEVA enrollment (i.e., enrollment was completed by proxy after the case died; n = 7).

2 Weighted for confounding (conditional on age [modeled with indicator variables corresponding to 5-year groups]), not missing baseline ALSFRS-R score (conditional on most recent ALS diagnosis category, symptom onset site, diagnostic delay [months; modeled with the natural logarithm of a linear term], and time from diagnosis to enrollment in the Registry [months; modeled with a restricted, quadratic spline with knots at 7.72, 13.24, 23.06, and 44.19 months based on percentiles of the distribution in the Registry cases not missing baseline ALSFRS-R score]), and participating in GENEVA (conditional on race/ethnicity, being a current patient of a VA Medical Center, most recent ALS diagnosis category, symptom onset site, diagnostic delay [months; modeled with linear, quadratic, and cubic terms], time from diagnosis to enrollment in the Registry [months; modeled with a linear term], and baseline ALSFRS-R score [modeled with a restricted, quadratic spline with knots at 12, 34, and 44 based on percentiles of the distribution in GENEVA cases]). 95% CIs were calculated with robust variance estimates.

3 Person-months calculated for time on study (i.e., the difference between the GENEVA enrollment date and the death date or July 25, 2013).

4 HRs and 95% CIs correspond to time since diagnosis accounting for late entry into the risk set at the GENEVA enrollment date.

5 Includes Coast Guard (deaths: n = 6; total: n = 8), Activated National Guard (deaths: n = 5; total: n = 6), Activated Reserves (deaths: n = 11; total: n = 17), Inactivated National Guard (deaths: n < 5; total: n < 5), Inactivated Reserves (deaths: n = 8; total: n = 9), Department of Defense (deaths: n = 0; total: n = 0), National Oceanic and Atmospheric Administration (deaths: n = 0; total: n < 5), and Public Health Service (deaths: n = 0; total: n = 0). Any numbers presented as “n < 5” were suppressed to preserve the confidentiality of study participants.

6 Used within-category medians that were calculated using all cases.

7 Scaled the HR to an IQR-unit increase in the exposure variable. IQRs were calculated using all cases.

8 Category boundaries aligned with the occurrence of the major wars (e.g., the Vietnam War occurred between August 1964 and May 1975) and followed Allen et al. [14], Beard et al. [17], and Schmidt et al. [15].

https://doi.org/10.1371/journal.pone.0185751.t003
Table 4. Military deployments or danger pay and amyotrophic lateral sclerosis survival in GENEVA\(^a\), United States of America, 2005–2013.

| Variable | Deaths | Total | IP-weighted\(^b\) |
|----------|--------|-------|-------------------|
|          | No. PM\(^c\) | No. PM\(^c\) | HR\(^d\) 95% CI\(^d\) |
| Deployments | | | |
| Ever deployed to any war/operation\(^e\) | | | |
| No | 250 | 5,790 | 348 | 13,683 | 1.00 | Referent |
| Yes | 179 | 4,472 | 247 | 9,986 | 0.98 | 0.78, 1.23 |
| Missing | 17 | | | 21 | |
| War/operation of longest deployment\(^e\) | | | |
| Not deployed | 250 | 5,790 | 348 | 13,683 | 1.00 | Referent |
| World War II | 24 | 671 | 29 | 1,076 | 1.97 | 1.34, 2.87 |
| Korean War | 29 | 686 | 32 | 931 | 0.96 | 0.41, 2.25 |
| Vietnam War | 98 | 2,318 | 138 | 5,474 | 1.02 | 0.75, 1.40 |
| Gulf War < 5\(^f\) | 164 | 114 | 762 | 0.38 | 0.12, 1.18 |
| Other\(^g\) | 15 | 421 | 24 | 1,164 | 0.81 | 0.43, 1.54 |
| Missing | 26 | | | 34 | |
| Ever deployed to any other country | | | |
| No | 222 | 5,222 | 309 | 12,310 | 1.00 | Referent |
| Yes | 205 | 5,014 | 283 | 11,254 | 1.01 | 0.81, 1.26 |
| Missing | 19 | | | 24 | |
| Total time (years) of all periods of deployment to any war/operation\(^e\) | | | |
| Not deployed (Median = 0.00) | 250 | 5,790 | 348 | 13,683 | 1.00 | Referent |
| \(< 1 \text{ (0.67)}\) | 83 | 2,030 | 120 | 4,976 | 1.01 | 0.86, 1.14 |
| \(1 \text{ to } 2 \text{ (1.25)}\) | 45 | 1,228 | 67 | 2,918 | 0.77 | 0.56, 1.06 |
| \(2 \text{ to } 4 \text{ (2.37)}\) | 29 | 643 | 36 | 1,238 | 1.45 | 1.01, 2.10 |
| \(> 4 \text{ (6.00)}\) | 8 | 183 | 11 | 417 | 0.64 | 0.19, 2.23 |
| Missing | 26 | | | 34 | |
| Trend\(^h\) | | | 0.87 | 0.71, 1.07 |
| End of most recent period of deployment to any war/operation (month/year)\(^i\) | | | | |
| Not deployed | 250 | 5,790 | 348 | 13,683 | 1.00 | Referent |
| \(< 06/1950 \text{ (01/1946)}\) | 23 | 656 | 28 | 1,061 | 1.74 | 1.16, 2.60 |
| \(07/1950-01/1955 \text{ (01/1953)}\) | 24 | 539 | 26 | 702 | 1.35 | 0.90, 2.03 |
| \(02/1955-02/1961 \text{ (02/1956)}\) | 7 | 165 | 8 | 247 | 1.94 | 0.48, 7.75 |
| \(03/1961-04/1975 \text{ (02/1969)}\) | 98 | 2,362 | 136 | 5,348 | 1.14 | 0.82, 1.58 |
| \(05/1975-07/1990 \text{ (08/1980)}\) | 6 | 147 | 10 | 491 | 1.00 | 0.53, 1.87 |
| \(> 07/1990 \text{ (07/1992)}\) | 12 | 391 | 25 | 1,462 | 0.58 | 0.30, 1.10 |
| Missing | 26 | | | 35 | |
| Trend (IQR = 14 years, 11.98 months)\(^h, i\) | | | 0.65 | 0.48, 0.89 |
| Danger pay, hardship duty or combat zone tax exclusion benefits for deployment | | | |
| Ever received imminent danger pay, hardship duty or combat zone tax exclusion benefits for deployment | | | |
| No | 309 | 7,571 | 414 | 16,134 | 1.00 | Referent |
| Yes | 103 | 2,267 | 157 | 6,498 | 0.87 | 0.66, 1.15 |
| Missing | 34 | | | 45 | |
| Total time (years) of all periods of deployment to any countries or sea region(s) ever received imminent danger pay, hardship duty or combat zone tax exclusion benefits for deployment | | | (Continued) |
### Table 4. (Continued)

| Variable | Deaths | Total | IP-weighted<sup>a</sup> |
|----------|--------|-------|------------------------|
|          | No. | PM<sup>b</sup> | No. | PM<sup>b</sup> | HR<sup>c</sup> | 95% CI<sup>c</sup> |
| Never received imminent danger pay, hardship duty or combat zone tax exclusion benefits for deployment (0.00) | 309 | 7,571 | 414 | 16,134 | 1.00 | Referent |
| ≤ 1 (0.83) | 47 | 1,092 | 73 | 3,104 | 0.80 | 0.52, 1.21 |
| > 1–2 (1.13) | 21 | 447 | 30 | 1,172 | 0.88 | 0.58, 1.33 |
| > 2 (2.50) | 8 | 191 | 11 | 462 | 1.00 | 0.48, 2.07 |
| Missing | 61 | 88 | | | 0.98 | 0.79, 1.22 |
| Trend<sup>d</sup> | | | | | | |

Abbreviation: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; CI, confidence interval; GENEVA, Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis study; Gulf, 1990–1991 Persian Gulf; HR, hazard ratio; IP, inverse probability; IQR, interquartile range; PM, person-months; VA, Department of Veterans Affairs.

<sup>a</sup> Fourteen ALS cases were excluded from this analysis because (1) they were missing data on diagnosis date (n = 7) or (2) they died before GENEVA enrollment (i.e., enrollment was completed by proxy after the case died; n = 7).

<sup>b</sup> Weighted for confounding (conditional on age [modeled with indicator variables corresponding to 5-year groups]), not missing baseline ALSFRS-R score (conditional on most recent ALS diagnosis category, symptom onset site, diagnostic delay [months; modeled with the natural logarithm of a linear term], and time from diagnosis to enrollment in the Registry [months; modeled with a restricted, quadratic spline with knots at 7.72, 13.24, 23.06, and 44.19 months based on percentiles of the distribution in the Registry cases not missing baseline ALSFRS-R score]), and participating in GENEVA (conditional on race/ethnicity, being a current patient of a VA Medical Center, most recent ALS diagnosis category, symptom onset site, diagnostic delay [months; modeled with linear, quadratic, and cubic terms], time from diagnosis to enrollment in the Registry [months; modeled with a linear term], and baseline ALSFRS-R score [modeled with a restricted, quadratic spline with knots at 12, 34, and 44 based on percentiles of the distribution in GENEVA cases]). 95% CIs were calculated with robust variance estimates.

<sup>c</sup> Person-months calculated for time on study (i.e., the difference between the GENEVA enrollment date and the death date or July 25, 2013).

<sup>d</sup> HRs and 95% CIs correspond to time since diagnosis accounting for late entry into the risk set at the GENEVA enrollment date.

<sup>e</sup> The GENEVA study questionnaire asked “Were you deployed to...” the following wars where each war was asked about with a separate question: World War II (defined as the period from December 7, 1941, to December 31, 1946), the Korean War (defined as the period from June 27, 1950, to January 31, 1955), the Vietnam War (defined as the period from August 3, 1964, to May 7, 1975), and the Persian Gulf War (defined as the period from August 2, 1990, to December 31, 1991) [16]. The questionnaire also asked “Ever deployed...” to the following countries where each country was asked about with a separate question: Grenada, Lebanon, Panama, Somalia, Bosnia, Kosovo, Rwanda, Afghanistan, and Iraq/Persian Gulf region (Gulf War II) [16].

<sup>f</sup> Suppressed to preserve the confidentiality of study participants.

<sup>g</sup> Includes Grenada (deaths: n = 0; total: n = 0), Lebanon (deaths: n < 5; total: n = 5), Panama (deaths: n < 5; total: n = 8), Somalia (deaths: n < 5; total: n < 5), Bosnia (deaths: n < 5; total: n < 5), Kosovo (deaths: n = 0; total: n = 0), Rwanda (deaths: n = 0; total: n = 0), Afghanistan (deaths: n < 5; total: n < 5), and Iraq/Persian Gulf region (Gulf War II) (deaths: n = 5; total: n = 6).

<sup>h</sup> Used within-category medians that were calculated using all cases.

<sup>i</sup> Category boundaries aligned with the occurrence of the major wars (e.g., the Vietnam War occurred between August 1964 and May 1975) and followed Allen et al. [14], Beard et al. [17], and Schmidt et al. [15].

<sup>j</sup> Scaled the HR to an IQR-unit increase in the exposure variable. IQRs were calculated using all cases except those in the reference category. Reference category excluded for linear trend test.

https://doi.org/10.1371/journal.pone.0185751.1004

(Table H in S1 File), control confounding by sex, or mitigate potential bias from exposure misclassification. Using age as the timescale, with late entry at GENEVA enrollment date, produced similar results. Recoding implausible values to missing for exposures that had distinct time periods of use removed the association between anthrax vaccination and shorter survival (HR = 0.99; 95% CI: 0.43, 2.26), but gave qualitatively similar results for the other three exposures. The majority of exposures were either not or only weakly correlated (absolute value of coefficients ≤ 0.2), and results were similar after mutually-adjusting correlated exposures. Finally, adjusting for potential confounding via standard regression methods, but without
### Table 5. Military exposures and amyotrophic lateral sclerosis survival in GENEVA\(^a\), United States of America, 2005–2013.

| Exposure                                                                 | Deaths          | Total          | IP-weighted$^{e, d}$ |
|--------------------------------------------------------------------------|-----------------|----------------|----------------------|
|                                                                          | No.  PM\(^b\)  | No.  PM\(^c\)  | HR\(^f\)  95% CI\(^f\) |
| Total                                                                    | 446  10,558    | 616  24,267    |                     |
| Ever received the anthrax vaccine prior to reference date                | 25   534       | 35   1,372     | 1.62  1.10, 2.40    |
| Ever received the smallpox vaccine                                       | 329  7,944     | 454  18,127    | 0.92  0.67, 1.26    |
| Prior to reference date, ever involved in testing, transporting or spraying herbicides for military purposes | 10   350       | 17   851       | 1.12  0.63, 1.99    |
| Prior to reference date, ever been treated with nasopharyngeal (NP) radium during military service | $< 5^\text{g}$ 96 | $< 5^\text{g}$ 179 | 0.97  0.59, 1.59    |
| Ever taken pyridostigmine bromide, or little white pills in foil packs, sometimes called NAPPs, which are used to protect against nerve agents | 10   296       | 18   940       | 1.21  0.42, 3.44    |
| Prior to reference date, ever visited or resided in the island of Guam, the islands of New Guinea, or the Kii Peninsula of Japan (including any time spent there in the military) | 66   1,619     | 90   3,550     | 1.00  0.76, 1.30    |
| While you were in WWII, the Korean War, the Vietnam War, or the Gulf War\(^h\): did you have direct contact with/were you exposed to |                     | 168  4,112     | 8,976               |
| Ionizing radiation from nuclear weapon testing or occupation of Hiroshima/Nagasaki | $< 5^\text{g}$ 18 | $< 5^\text{g}$ 77 | 1.01  0.22, 4.75    |
| Use of personal pesticides, like creams, sprays or flea collars          | 50   1,206     | 67   2,536     | 0.91  0.62, 1.33    |
| Use of pesticides on your clothing or bedding                           | 36   675       | 49   1,673     | 1.05  0.63, 1.77    |
| Exhaust from heaters or generators (e.g., kerosene heaters, tent heaters) | 52   1,213     | 74   3,035     | 0.81  0.53, 1.21    |
| Exposure to diesel and/or other petrochemical fumes                     | 102  2,499     | 143  5,750     | 1.06  0.66, 1.72    |
| Burning trash or burning feces/manure                                    | 51   1,243     | 74   3,096     | 0.80  0.54, 1.19    |
| Exposure to paint, solvents, or petrochemical substances                | 45   1,132     | 72   3,264     | 0.73  0.50, 1.06    |
| High-intensity radar waves (e.g., as radar operator, radio operator, aviation electrician’s mate) | 35   815       | 46   1,692     | 1.32  0.91, 1.92    |
| Food contaminated with smoke, oil, or other chemicals                   | 11   267       | 15   580       | 0.71  0.36, 1.40    |
| Local food other than food provided by the Armed Forces                  | 77   2,056     | 112  4,873     | 0.68  0.49, 0.93    |
| Bathing in or drinking of water contaminated with smoke, oil, dead animals or any chemicals | 12   188       | 20   801       | 0.85  0.33, 2.21    |
| Heat cramps, heat exhaustion, heat stroke or other heat illness          | 34   811       | 50   2,103     | 0.88  0.54, 1.44    |
| Heard chemical alarms sounding                                          | 7    169       | 15   810       | 0.59  0.25, 1.40    |
| Explosion in the air or on the ground within one mile of you (e.g., artillery, rockets, mortars) | 112  2,601     | 149  5,597     | 1.27  0.87, 1.84    |
| Have you suffered a combat-related injury that required medical attention during your deployment? | 38   1,015     | 49   1,871     | 0.88  0.54, 1.44    |
| While you were in WWII, the Korean War, the Vietnam War, or the Gulf War\(^h\): did you have direct contact with/were you exposed to |                     | 164  3,992     | 8,164               |
| Mixing and application of herbicides                                    | $< 5^\text{g}$ 87 | $< 5^\text{g}$ 87 | 1.57  0.99, 2.51    |
| Exposure to herbicides in the field                                     | 10   304       | 11   396       | 1.02  0.62, 1.66    |
| Mixing and application of riot control substances                       | $< 5^\text{g}$ 9 | $< 5^\text{g}$ 9 | 4.30  2.33, 7.94    |
| Exposure to riot control substances in the field                        | 9    267       | 12   490       | 0.63  0.32, 1.21    |
| Mixing and application of burning agents                                | 13   193       | 14   284       | 2.57  1.28, 5.12    |
| Exposure to burning agents in the field                                 | 22   511       | 32   1,271     | 0.56  0.35, 0.91    |
| While you were in the Korean War, the Vietnam War, or the Gulf War\(^h\): did you have direct contact with/were you exposed to |                     | 141  3,384     | 7,659               |
| Microwave radiation                                                     | 10   241       | 14   581       | 1.03  0.62, 1.69    |
| While you were in the Vietnam War\(^h\): did you have direct contact with/were you exposed to |                     | 104  2,492     | 5,739               |

(Continued)
weighting for potential missing-covariate-data or selection bias, gave results that were generally similar ("Adjusted" columns, Tables B-G and I-K in S1 File).

### Discussion

We found shorter survival among cases who served ≤ 1 year in the military, served or were deployed before July 1950 or in WWII, and mixed and applied burning agents. In contrast,
survival was longer among cases who were exposed to: paint, solvents, or petrochemical substances; local food not provided by the Armed Forces; or burning agents and Agent Orange in the field. We obtained similar results from several secondary analyses, such as restricting to cases who: enrolled within two years of diagnosis; had definite or probable ALS; were men; or did not need a proxy interview.

Some evidence suggests ALS diagnoses may be increased among military veterans, particularly those deployed to the Gulf War [7–10]. However, few studies have evaluated associations between military-related or other environmental or occupational factors and ALS progression or survival, and they all have important limitations [4–6, 11, 12]. The study based on the ALS Clinical Assessment, Research and Education database [11] was published in abstract form only, so it is difficult to evaluate. The Massachusetts study [6], which also reported no association between one-year disease progression and exposure to several toxicants evaluated as a group, did not adjust for age at diagnosis, which is one of the most consistently reported prognostic factors for ALS survival [2–5]. The studies by Kasarskis et al. [12] and Pastula et al. [5], which examined war deployments, were susceptible to immortal person-time bias. The discrepant results of these studies may be because the first—which found a positive association—was restricted to Gulf War-era veterans [12], whereas the other—which found no association—included non-Gulf War-era veterans [5]. Like Pastula et al. [5], our study included a subset of Registry cases who served as far back as WWII. Unlike Pastula et al. [5], we found shorter survival among cases who were deployed to WWII, but not to other wars/operations, compared to non-deployed cases.

Our finding of an association between anthrax vaccination and shorter survival may be partly due to reporting errors; some veterans who reported receiving the vaccination served in the military in the 1950s [17], but the vaccination was not available until 1998 [46]. Recoding implausible values to missing removed the association. Our finding of shorter survival among cases who mixed and applied burning agents contrasts with the longer survival we observed among cases who experienced field exposure to burning agents. Mixing and applying, however, may have resulted in greater exposure than field exposure and was also likely less susceptible to recall bias. Our finding of positive exposure-response trends between pyridostigmine bromide pills and survival was limited by small numbers of deaths in exposure categories and should be interpreted cautiously. The elevated HR observed for high-intensity radar waves is consistent with reports that non-ionizing radiation may be associated with ALS etiology [47]. One explanation for associations we observed between longer survival and exposure to: paint, solvents, or petrochemical substances; local food; or Agent Orange in the field is individuals who were susceptible to these exposures may have died before Registry enrollment. However, we found no relationship between these exposures and diagnostic delay, symptom onset site, or baseline ALSFRS-R score, which were clinical factors consistently reported to be associated with shorter survival by previous studies [2–6].

Residual confounding by age may have affected our results because cases who served before July 1950 or were deployed to WWII were more than 70 years-old in 2005–2010 when GENEVA was conducted [15] and were thus more likely to die during follow-up. Using age as the timescale, with late entry at GENEVA enrollment date, however, gave similar results. It is also possible other exposures experienced during military service or civilian life confounded associations we observed between survival and specific exposures experienced during deployment to the four wars. We did not adjust for non-military exposures, but results were similar after mutually-adjusting correlated military exposures, which mitigates this concern.

The positive association we observed between ALS survival and time from enrollment in the Registry to enrollment in GENEVA is perplexing. This result was meant to be descriptive
and, therefore, was adjusted for age at diagnosis via standard regression methods, but was not weighted for potential missing-covariate-data or selection biases. It is possible that this result is due to selection bias. In other words, it is possible that the patients with the fastest progressing ALS died after they enrolled in the Registry, but before they enrolled in GENEVA (Table A in S1 File). This would create the appearance of a positive association between ALS survival and time from enrollment in the Registry to enrollment in GENEVA among ALS cases who enrolled in GENEVA.

The four assumptions for using weights for analysis are consistency, exchangeability (i.e., no unmeasured confounding, missing data, or selection bias), no misspecification of models used to estimate the weights, and positivity [31]. Consistency is not empirically verifiable, but is often assumed to hold [31]. As described above, we explored exchangeability by conducting secondary analyses in which we restricted to men only and mutually-adjusted correlated military exposures. We attempted to minimize model misspecification by using the Akaike Information Criterion [48] to select the form (e.g., linear, categorical, spline, etc.) for each continuous variable included in our models for the weights [49] (Section C in S1 File). To explore positivity, we created cross-tabulations of the military-related factors and age and war/operation of deployment (for military exposures).

We also inspected appropriateness of the weights we used in our analyses. Most means of the overall stabilized weights were near one and there were few extreme weights. Exceptions generally occurred among time-related variables (e.g., end of most recent service or deployment). Cross-tabulations of the affected variables and age revealed empty cells—especially in extreme combinations of the variables and age. These instances of empty cells are likely structural rather than random [31], because, for example, WWII veterans would not have been ≤ 39 years-old when GENEVA was conducted. We remedied the problem by collapsing categories of both the affected variables and age and obtained HRs and 95% CIs that were similar to those we obtained when we used the expanded versions.

Our results do not generalize to veteran cases who died before enrollment in the Registry began in 2003 [5] or who did not join the Registry for other reasons [17] because we were only able to weight GENEVA cases to represent Registry cases. In addition, the median (IQR) time from enrollment in the Registry to enrollment in GENEVA was nine (11) months, which is a short interval relative to elapsed time since diagnosis for cases who were long-term survivors. Thus, our results could have been affected by residual selection bias.

There are limitations to studying cases from the Registry. For example, the Registry contains incident cases and prevalent cases that include some long-term survivors [15, 50]. In addition, as among non-deployed veterans in the VA’s previous Gulf War ALS study [8, 10], the Registry likely under-ascertained cases [17] notwithstanding a national recruiting effort [14]. Despite these limitations, we observed associations between clinical and demographic characteristics and ALS survival that agreed with previous literature—e.g., HRs for death decreased with increases in diagnostic delay [2, 5, 6] and baseline ALSFRS-R score [2, 3] and were higher among older cases [2–5]—increasing confidence in our results.

We collected information on military-related factors via standardized telephone interviews [15, 16] because of the lack of suitable exposure biomarkers and sufficiently detailed military databases for most exposures we evaluated in our study [17]. Several studies have evaluated the validity and reliability of many self-reported military-related factors, usually in comparison to data from the U.S. Department of Defense’s Defense Manpower Data Center, and reported concordances to range from “moderate” (e.g., $\kappa = 0.41–0.60$) to “almost perfect” (e.g., $\kappa > 0.80$) [10, 46, 51–58]. Validity studies evaluated deployment status and frequency, number, and start dates of deployment(s) [10, 56]; occupational titles [57]; and anthrax [46, 54] or smallpox vaccination [53]. Military-related factors evaluated in reliability
studies included combat-related experiences, exposures, or traumatic events [51, 52, 55, 58] and exposure indices constructed by averaging or summing participants’ answers for specific items [51, 52, 55, 58]. Unfortunately, none of these studies assessed the validity or reliability of self-reported military-related factors extending back to WWII (the longest time between exposure and assessment of exposure in these studies was about 10 years [10]) or whether the quality of self-report fluctuated by time period of service or war/operation of deployment.

Although the validity and reliability of self-report has not been determined for many of the military-related factors we evaluated in our study, we would typically expect military service factors, such as branch of service or rank, to be more validly and reliably reported than military deployment factors, such as war/operation of deployment or dates of deployment, which would likely be more validly and reliably reported than specific military exposures [17]. In fact, this is the pattern typically described by other occupational epidemiology studies (i.e., job title is typically more validly and reliably reported than dates of employment or job tasks, which are typically more validly and reliably reported than specific occupational exposures) [59].

Strategies to improve recall for GENEVA included asking participants about exposures that can be sensed (e.g., heard chemical alarms sounding), using general terms (e.g., flea collar rather than specific pesticides), querying a list of specific exposures, and providing benchmarks against which respondents could compare their exposure levels (e.g., feeling ill after exposure) [15]. Despite using these strategies, we found some reporting errors for a few exposures with distinct time periods of use. When we set implausible values to missing, however, results were qualitatively similar for exposures other than anthrax vaccination. Importantly, results were similar after restricting to non-proxy interviews.

Strengths of our study include medical record-confirmed diagnoses and relatively complete ascertainment of deaths from VA sources. We also had a large sample size, although the number of deceased cases who experienced some exposures, particularly Gulf War-specific ones, was small. We had extensive information on military service, deployments, and 39 related exposures. Given the large number of exposures for which we evaluated associations with ALS survival and the hypothesis-generating nature of our study, it is possible that some of the associations we observed may not be true. However, we obtained similar results from sub-analyses that created a more homogeneous sample or attempted to reduce potential biases. Finally, we used inverse probability weights to explore and control potential biases from confounding, missing covariate data, and selection among a case group that included a disproportionate number of long-term survivors at enrollment.

Conclusions
In conclusion, this is one of the first and largest studies, and the most complete, to date of ALS survival and non-clinical factors—specifically those related to military service. It includes both detailed exposure assessment and sophisticated analytic approaches to minimize bias. Although we observed associations with clinical and demographic characteristics that agreed with previous literature, most military-related factors were not associated with ALS survival. Associations we observed between shorter survival and certain exposures, such as burning agents, although novel and needing confirmation, are potentially important because of the large number of U.S. military veterans. Furthermore, they could help clinicians target interventions that may have the potential to lengthen survival among patients at greatest risk of shorter survival.
Supporting information
S1 File. (DOCX)

Acknowledgments
We thank the participants in GENEVA without whom the study would have been impossible. We thank Lydia Kwee, Marcus Johnson, Cynthia Coffman, Jennifer Lindquist, Eugene Oddone, and Dawn Provenzale for helping us obtain data from GENEVA and the National Registry of Veterans with ALS. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs or the United States Government.

Author Contributions
Conceptualization: John D. Beard, Kelli D. Allen, Silke Schmidt, Freya Kamel.
Data curation: John D. Beard, Jean Keller.
Formal analysis: John D. Beard, Lawrence S. Engel, David B. Richardson, Marilie D. Gammon, Jean Keller, Freya Kamel.
Funding acquisition: Dale P. Sandler, Silke Schmidt.
Investigation: Kelli D. Allen, Catherine L. Stanwyck, Silke Schmidt.
Methodology: John D. Beard, Lawrence S. Engel, David B. Richardson, Marilie D. Gammon, Kelli D. Allen, Jean Keller, Silke Schmidt, Freya Kamel.
Project administration: Kelli D. Allen, Catherine L. Stanwyck, Silke Schmidt, Freya Kamel.
Resources: John D. Beard, Kelli D. Allen, Catherine L. Stanwyck, Jean Keller, Silke Schmidt.
Software: John D. Beard, Jean Keller.
Supervision: Lawrence S. Engel, Kelli D. Allen, Silke Schmidt, Freya Kamel.
Visualization: John D. Beard.
Writing – original draft: John D. Beard.
Writing – review & editing: John D. Beard, Lawrence S. Engel, David B. Richardson, Marilie D. Gammon, Coleen Baird, David M. Umbach, Kelli D. Allen, Catherine L. Stanwyck, Jean Keller, Dale P. Sandler, Silke Schmidt, Freya Kamel.

References
1. Mitchell JD, Borasio GD. Amyotrophic lateral sclerosis. Lancet. 2007; 369: 2031–2041. PMID: 17574095
2. Chio A, Logroscino G, Hardiman O, Swingler R, Mitchell D, Beghi E, et al. Prognostic factors in ALS: a critical review. Amyotroph Lateral Scler. 2009; 10: 310–323. https://doi.org/10.3109/17482960802966824 PMID: 19922118
3. Gordon PH, Cheng B, Salachas F, Pradat PF, Bruneteau G, Corcia P, et al. Progression in ALS is not linear but is curvilinear. J Neurol. 2010; 257: 1713–1717. https://doi.org/10.1007/s00415-010-5609-1 PMID: 20332945
4. Mandrioli J, Faglioni P, Nichelli P, Sola P. Amyotrophic lateral sclerosis: prognostic indicators of survival. Amyotroph Lateral Scler. 2006; 7: 211–220. PMID: 17127559
5. Pastula DM, Coffman CJ, Allen KD, Oddone EZ, Kasarskis EJ, Lindquist JH, et al. Factors associated with survival in the National Registry of Veterans with ALS. Amyotrophic Lateral Sclerosis. 2009; 10: 332–338. https://doi.org/10.3109/17482960802320545 PMID: 19922120

6. Qureshi MM, Hayden D, Urbinelli L, Ferrante K, Newhall K, Myers D, et al. Analysis of factors that modify susceptibility and rate of progression in amyotrophic lateral sclerosis (ALS). Amyotrophic Lateral Sclerosis. 2006; 7: 173–182. PMID: 16963407

7. Beard JD, Kamel F. Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis etiology and survival. Epidemiol Rev. 2015; 37: 55–70. https://doi.org/10.1093/epirev/mxu001 PMID: 25365170

8. Coffman CJ, Horner RD, Grambow SC, Lindquist J, V.A. Cooperative Studies Program Project #500. Estimating the occurrence of amyotrophic lateral sclerosis among Gulf War (1990–1991) veterans using capture-recapture methods. Neuroepidemiology. 2005; 24: 141–150. PMID: 15650320

9. Haley RW. Excess incidence of ALS in young Gulf War veterans. Neurology. 2003; 61: 750–756. PMID: 14504316

10. Horner RD, Kamins KG, Feussner JR, Grambow SC, Hoff-Lindquist J, Harati Y, et al. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. Neurology. 2003; 61: 742–749. PMID: 14504315

11. Brooks BR, Anderson FA, Gowda N, ALS CARE Study Group. Amyotrophic lateral sclerosis (ALS) outcomes in US military veterans compared with non-veterans: neuroepidemiological insights from the ALS CARE Database [abstract]. Amyotrophic Lateral Sclerosis Other Motor Neuron Disorder. 2003; 4: 114.

12. Kasarskis EJ, Lindquist JH, Coffman CJ, Grambow SC, Feussner JR, Allen KD, et al. Clinical aspects of ALS in Gulf War veterans. Amyotrophic Lateral Sclerosis. 2009; 10: 35–41. https://doi.org/10.1080/17482960802351029 PMID: 18792848

13. Miller RG, Anderson FA Jr., Bradley WG, Brooks BR, Mitsumoto H, Munsat TL, et al. The ALS patient care database: goals, design, and early results. Neurology. 2000; 54: 53–57. PMID: 10636125

14. Allen KD, Kasarskis EJ, Bediack RS, Rozear MP, Morgenlander JC, Sabet A, et al. The National Registry of Veterans with Amyotrophic Lateral Sclerosis. Neuroepidemiology. 2008; 30: 180–190. https://doi.org/10.1159/000126910 PMID: 18421219

15. Schmidt S, Allen KD, Loiacono VT, Norman B, Stanwyck CL, Nord KM, et al. Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis: the GENEV A study. Rationale, study design and demographic characteristics. Neuroepidemiology. 2008; 30: 191–204. https://doi.org/10.1159/000126911 PMID: 18421219

16. Beard JD. Military Service, Deployments, and Exposures in Relation to Amyotrophic Lateral Sclerosis Etiology and Survival. ETD Dissertation, University of North Carolina at Chapel Hill. 2015.

17. Beard JD, Engel LS, Richardson DB, Gammon MD, Baird C, Umbach DM, et al. Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis etiology. Environ Int. 2016; 91: 104–115. https://doi.org/10.1016/j.envint.2016.02.014 PMID: 26923711

18. Kasarskis EJ, Dominic K, Oddone EZ. The National Registry of Veterans with Amyotrophic Lateral Sclerosis: Department of Veterans Affairs Cooperative Studies Program (CSP) #500a. Amyotrophic Lateral Sclerosis Other Motor Neuron Disorder. 2004; 5: 129–132. PMID: 15512895

19. World Health Organization. International Statistical Classification of Diseases and Related Health Problems. Geneva, Switzerland: World Health Organization; 1977.

20. Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis Other Motor Neuron Disorder. 2000; 1: 293–299. PMID: 11464847

21. Lash TL, Cole SR. Immortal person-time in studies of cancer outcomes. J Clin Oncol. 2009; 27: e55–56. https://doi.org/10.1200/JCO.2009.24.1877 PMID: 19597013

22. Gordon PH, Corcia P, Lacomblez L, Pochigaeva K, Abitbol JL, Cudkowicz M, et al. Defining survival as an outcome measure in amyotrophic lateral sclerosis. Arch Neuro. 2009; 66: 758–761. https://doi.org/10.1001/archneurol.2009.1 PM id: 19506136

23. Arnold N, Sohn M, Maynard C, Hynes DM. ViReC Technical Report 2: VA-NDI Mortality Data Merge Project. Hines, IL: Department of Veteran Affairs, Edward Hines, Jr. VA Hospital; 2006.

24. National Center for Health Statistics, Center for Disease Control and Prevention. National Death Index Homepage. National Center for Health Statistics; 2013. http://www.cdc.gov/nchs/ndi.htm. Accessed: February 6, 2013.

25. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hill D, Thurmond B, et al. The ALSFRS-R-a revised ALS functional rating scale that incorporates assessments of respiratory function. J Neurol Sci. 1999; 169: 13–21. PMID: 10540002
26. Doebbeling BN, Jones MF, Hall DB, Clarke WR, Woolson RF, Torner JC, et al. Methodologic issues in a population-based health survey of Gulf War veterans. J Clin Epidemiol. 2002; 55: 477–487. PMID: 12007551
27. Ryan MA, Smith TC, Smith B, Amoroso P, Boyko EJ, Gray GC, et al. Millennium Cohort: enrollment begins a 21-year contribution to understanding the impact of military service. J Clin Epidemiol. 2007; 60: 181–191. PMID: 1720125
28. Smith TC, Millennium Cohort Study Team. The US Department of Defense Millennium Cohort Study: career span and beyond longitudinal follow-up. J Occup Environ Med. 2009; 51: 1193–1201. https://doi.org/10.1097/JOM.0b013e3181873146 PMID: 1976902
29. Allison PD. Survival Analysis Using SAS: A Practical Guide. Cary, NC: SAS Institute, Inc.; 2010.
30. Greeneland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999; 10: 37–48. PMID: 9888278
31. Cole SR, Heman MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol. 2008; 168: 656–664. https://doi.org/10.1093/aje/kwn164 PMID: 18682488
32. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999; 10: 37–48. PMID: 9888278
33. Robins JM, Hernan MA, Brumbach B. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology. 2000; 11: 561–570. PMID: 10955409
34. Greeneland S. Introduction to regression models. In: Rothman KJ, Greenland S, Lash TL, editors. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott, Williams, & Wilkins; 2008. pp. 381–417.
35. Goldberg M, Silbergeil E. On multiple comparisons and on the design and interpretation of epidemiologic studies of many associations. Environ Res. 2011; 111: 1007–1009. https://doi.org/10.1016/j.envres.2011.08.010 PMID: 21906734
36. Greenland S. Multiple comparisons and association selection in general epidemiology. Int J Epidemiol. 2008; 37: 430–434. https://doi.org/10.1093/ije/dyn064 PMID: 18453632
37. Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology. 1990; 1: 43–46. PMID: 2081237
38. Savitz DA, Oshlan AF. Multiple comparisons and related issues in the interpretation of epidemiologic data. Am J Epidemiol. 1995; 142: 904–908. PMID: 7572970
39. Thompson JR. Invited commentary: Re: “Multiple comparisons and related issues in the interpretation of epidemiologic data”. Am J Epidemiol. 1998; 147: 801–806. PMID: 9583708
40. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B. 1995; 57: 289–300.
41. Greenland S, Robins JM. Empirical-Bayes adjustments for multiple comparisons are sometimes useful. Epidemiology. 1991; 2: 244–251. PMID: 1912039
42. Witte JS, Greenland S, Kim LL. Software for hierarchical modeling of epidemiologic data. Epidemiology. 1998; 9: 563–566. PMID: 9790038
43. O’Brien KM, Cole SR, Poole C, Benson JT, Herring AH, Engel LS, et al. Replication of breast cancer susceptibility loci in whites and African Americans using a Bayesian approach. Am J Epidemiol. 2014; 179: 382–394. https://doi.org/10.1093/aje/kw258 PMID: 24218030
44. Smith B, Leard CA, Smith TC, Reed RJ, Ryan MA, Millennium Cohort Study Team. Anthrax vaccination in the Millennium Cohort: validation and measures of health. Am J Prev Med. 2007; 32: 347–353. https://doi.org/10.1016/j.amepre.2006.12.015 PMID: 17383567
45. Vergha X, Kheifets L, Greeneland S, Okusuyn S, Cho YS, Mezeg G. Occupational exposure to extremely low-frequency magnetic fields and neurodegenerative disease: a meta-analysis. J Occup Environ Med. 2013; 55: 135–146. https://doi.org/10.1097/JOM.0b013e3182737378 PMID: 23989409
46. Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr. 1974; 19: 716–723.
47. Howse CJ, Cole SR, Westreich D, Greeneland S, Napravnik S, Eron JJ Jr. Splines for trend analysis and continuous confounder control. Epidemiology. 2011; 22: 874–875. https://doi.org/10.1097/EDE. 0b013e318230209d PMID: 21987779
48. Schmidt S, Kwee LC, Allen KD, Oddone EZ. Association of ALS with head injury, cigarette smoking and APOE genotypes. J Neurol Sci. 2010; 291: 22–29. https://doi.org/10.1016/j.jns.2010.01.011 PMID: 20129626
51. Bramsen I, Dirkzwager AJ, van Esch SC, van der Ploeg HM. Consistency of self-reports of traumatic events in a population of Dutch peacekeepers: reason for optimism? J Trauma Stress. 2001; 14: 733–740. https://doi.org/10.1023/A:1013090005246 PMID: 11776420

52. Janes GR, Goldberg J, Eisen SA, True WR. Reliability and validity of a combat exposure index for Vietnam era veterans. J Clin Psychol. 1991; 47: 80–86. PMID: 2026782

53. LeardMann CA, Smith B, Smith TC, Wells TS, Ryan MA, Millennium Cohort Study Team. Smallpox vaccination: comparison of self-reported and electronic vaccine records in the millennium cohort study. Hum Vaccin. 2007; 3: 245–251. PMID: 17700077

54. Mahan C. Anthrax vaccination and self-reported symptoms, functional status, and medical conditions in the National Health Survey of Gulf War Era Veterans and Their Families. Ann Epidemiol. 2004; 14: 81–88. https://doi.org/10.1016/S1047-2797(03)00124-8 PMID: 15018879

55. Roemer L, Litz BT, Orsillo SM, Ehlich PJ, Friedman MJ. Increases in retrospective accounts of warzone exposure over time: the role of PTSD symptom severity. J Trauma Stress. 1998; 11: 597–605. https://doi.org/10.1023/A:1024469116047 PMID: 9690197

56. Smith B, Wingard DL, Ryan MA, Macera CA, Patterson TL, Slymen DJ. U.S. military deployment during 2001–2006: comparison of subjective and objective data sources in a large prospective health study. Ann Epidemiol. 2007; 17: 976–982. https://doi.org/10.1016/j.annepidem.2007.07.102 PMID: 17923418

57. Smith TC, Jacobson IG, Smith B, Hooper TI, Ryan MA, Millennium Cohort Study Team. The occupational role of women in military service: validation of occupation and prevalence of exposures in the Millennium Cohort Study. Int J Environ Health Res. 2007; 17: 271–284. https://doi.org/10.1080/09603120701372243 PMID: 17613091

58. Southwick SM, Morgan CA 3rd, Nicolaou AL, Charney DS. Consistency of memory for combat-related traumatic events in veterans of Operation Desert Storm. Am J Psychiatry. 1997; 154: 173–177. https://doi.org/10.1176/ajp.154.2.173 PMID: 9016264

59. Teschke K, Olsan AF, Daniels JL, De Roos AJ, Parks CG, Schulz M, et al. Occupational exposure assessment in case-control studies: opportunities for improvement. Occup Environ Med. 2002; 59: 575–593; discussion S94. https://doi.org/10.1136/oem.59.9.575 PMID: 12205230