Published in final edited form as:

Epidemiology. 2017 March ; 28(2): e15–e16. doi:10.1097/EDE.0000000000000589.

Military service and amyotrophic lateral sclerosis in a population-based cohort: extended follow-up 1979–2011

Jacquelyn J. Cragg[1], **Norman J. Johnson**[2], and **Marc G. Weisskopf**[1,3]

[1]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA

[2]Center for Administrative Records and Applications, US Bureau of the Census, Washington, DC

[3]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

To the Editor

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative neurological disease that leads to muscle wasting and paralysis, and eventually respiratory failure. Although there are familial cases of ALS, the vast majority of cases are sporadic and of unknown cause. One etiologic factor that has garnered much interest with respect to ALS is military service.[1–6]

A previous analysis of 1,089,314 individuals in the National Longitudinal Mortality Study (NLMS) followed up through 2002 revealed an association with military service and ALS that was specific for service in World War II (WWII).[4] Service during other conflicts, however, showed no association with ALS. To examine whether this period-specific association was related to longer follow-up among WWII veterans, we examined the relationship between military service and ALS risk in extended follow-up (and recruitment) of the NLMS through 2011.

This work was approved by the Institutional Review Board of the Harvard T.H. Chan School of Public Health. The NLMS, a representative sample of the civilian non-institutionalized population of the United States, was the primary data source used in this study as described previously.[4] Briefly, it is a survey of households (homeless individuals were thus excluded) and we restricted the population to those who were 25 years of age or older at the time of the survey (to better ensure that participants who served in the military would have done so by the time of their survey) and who responded to the questions regarding military service. Respondents were asked whether each household member had served in the U.S. military and the period of service. The National Death Index (NDI) was linked to the NLMS data, for the years 1979 through 2011, and identified ALS deaths via International Classification of Diseases (ICD) codes (ICD-9 335.2 before 1999; ICD-10 G12.2 after). Participants contributed follow-up time from the time of their survey or, for those surveyed before 1979, 1 January, 1979 (the start of electronic NDI data) until the time of death or the last date of

Correspondence to: Marc G. Weisskopf, Department of Environmental Health, Harvard T.H. Chan School of Public Health, Landmark Center, 3rd Floor East, P.O. Box 15697, Boston, MA 02215, mweissko@hsph.harvard.edu, Phone: 617.384.8872.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

NDI linkage. Mean values are presented with corresponding standard deviations (SDs). We used Cox proportional hazards modeling (using weighted data as described previously[4]) with age as the time metameter to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for ALS mortality.

In total, there were 1,007,913 NLMS male participants (15,242,189 person-years of follow-up; average follow-up: 15.1±10.3 years per person), among whom there were 643 ALS deaths. There was an elevated hazard ratio (HR) for military service among men that was restricted to men who served during WWII (Table). These general patterns held for females although there were fewer females (7,876,210 person years of follow-up; average follow-up: 10.7±7.3 years per person), and therefore wider CIs (eTable 1, Supplemental Digital Content).

To assess possible cohort and period effects, we first ran analyses (among men only) restricted to the principal birth years of people serving in each war era (WWII: 1907–1928; Korea: 1925–1936; Vietnam: 1935–1958; see eAppendix, Supplemental Digital Content). The results did not change appreciably (WWII HR: 1.5; 95% CI: 1.1–2.0; eTable 2, Supplemental Digital Content). When analyses were further stratified by quartiles of age at the time of survey, results for all war eras in the oldest age quartile were lower than the rest, but otherwise generally similar. The only noticeable difference was an elevated HR for Vietnam era service in the youngest quartile (<36 at survey: 49 ALS deaths total; HR 1.8; 95% CI: 1.0–3.3; eTable 3, Supplemental Digital Content).

In our extended follow-up, we did not find evidence for associations between periods of service other than WWII and ALS, although we cannot rule out an increased risk among veterans of the Persian Gulf, suggested in other studies,[5,6] because there were too few of those veterans in our cohort. Reduced associations in the oldest age quartiles of cohort and period stratified analyses could reflect survival bias. The stronger association with Vietnam service in the youngest age at survey quartile could relate to a time-limited association with Vietnam era service, or informative loss of Vietnam era veterans with age (see eAppendix, Supplemental Digital Content).

Our data strengthen the conclusion that something specific to WWII appears related to increased risk of ALS, although they raise the possibility of an association with Vietnam era service that deserves further attention. Of the several etiologic factors raised in prior studies of military service[7], our study suggests that those *not* specific to WWII don't explain our findings, including traumatic injuries, strenuous activity, viral infections, and lead exposure.[1] Ionizing radiation exposure (i.e., veterans involved in nuclear testing or clean-up) is one potential environmental exposure specific to WWII, though a case-control study in Japan found no such association.[8] Future research with data on such specific exposures is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

SOURCES OF FUNDING

This work was supported by grant #MDA239243 from the Muscular Dystrophy Association, NIH grant #NS 082105, and funding from the Agency for Toxic Substances and Disease Registry's National ALS Registry program. J. Cragg is supported by the ALS Canada Tim E. Noel Postdoctoral Fellowship, the Michael Smith Foundation for Health Research (MSFHR), and the Constance Livingstone-Friedman and Sydney Friedman Foundation Scholarship in Health Science.

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; nor in the decision to submit the manuscript for publication.

This paper is released to inform interested parties of research and to encourage discussion. Any views expressed on statistical, methodological, technical, or operational issues are those of the authors and not necessarily those of the U.S. Census Bureau.

REFERENCES

1. Beard JD, Kamel F. Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis etiology and survival. Epidemiol Rev. 2015; 37:55–70. [PubMed: 25365170]
2. Seals RM, Kioumourtzoglou MA, Gredal O, Hansen J, Weisskopf MG. ALS and the Military: A Population-Based Study in the Danish Registries. Epidemiology. 2015
3. Weisskopf MG, O'Reilly EJ, McCullough ML, et al. Prospective study of military service and mortality from ALS. Neurology. 2005; 64(1):32–37. [PubMed: 15642900]
4. Weisskopf MG, Cudkowicz ME, Johnson N. Military Service and Amyotrophic Lateral Sclerosis in a Population-based Cohort. Epidemiology. 2015; 26(6):831–838. [PubMed: 26414854]
5. Haley RW. Excess incidence of ALS in young Gulf War veterans. Neurology. 2003; 61(6):750–756. [PubMed: 14504316]
6. Horner RD, Kamins KG, Feussner JR, et al. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. Neurology. 2003; 61(6):742–749. [PubMed: 14504315]
7. Mitchell JD. Amyotrophic lateral sclerosis: toxins and environment. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000; 1(4):235–250. [PubMed: 11465017]
8. Kondo K, Tsubaki T. Case-control studies of motor neuron disease: association with mechanical injuries. Arch Neurol. 1981; 38(4):220–226. [PubMed: 7011280]

TABLE

Hazard Ratios for ALS by Military Service Among Men

	No. ALS Deaths (Total=643)	No. Followed (Total= 1,007,913)	Adjusted[a] HR (95% CI)
Veteran			
Yes	358	331,001	1.1 (1.0, 1.3)
No	285	676,912	Reference
Period of Service			
WWI[b]	0	2585	-
WWII	185	97,128	1.3 (1.1, 1.6)
Korean War	68	55,227	1.0 (0.8, 1.4)
Vietnam War	56	106,164	1.0 (0.7, 1.3)
Persian Gulf War[b,c]	0	7693	-
Other	49	62,204	1.1 (0.8, 1.5)
No Service	285	676,912	Reference

[a]Adjusted for age (time metameter), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic other), education (less than high school, high school, some college, college, postgraduate), and percent poverty (the ratio of the actual family income to the poverty threshold defined by the number of people in the household; <=200%, 201–300%, 301–500%, >500%).

[b]There were no ALS deaths in these groups, thus a HR could not be estimated

[c]Includes any war in this region since 2000

Abbreviations: CI=confidence interval; HR=hazard ratio; WWI= World War I, WWII= World War II; ALS= amyotrophic lateral sclerosis