Retrospective Assessment of Military Occupations & Neurodegenerative Diseases

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List of terms and abbreviations

ALS – amyotrophic lateral sclerosis
PD – Parkinson's disease
Neurodegenerative disease
Case-control study

Abstract

Recent findings from epidemiologic studies suggest that military service may a risk factor for the development of a later-life neurodegenerative disease, amyotrophic lateral sclerosis (ALS). The primary objective of this project was to determine whether military service is associated with the risk of developing ALS or another late-life neurodegenerative diseases, Parkinson's disease (PD). We examined the association between military service and the risk of developing PD and ALS using data from four recently completed community-based case-control studies conducted in Northern California and Western Washington State.

Amyotrophic Lateral Sclerosis Findings. Prior military service was very common among men with ALS in our studies, occurring among 56% of male controls in both studies, however, we observed no association of military service with ALS, either in the combined studies analysis or for either study separately. No dose-response relation with increasing years of military service was observed, and men who served only during wartime were not at an increased risk of ALS, nor were men who served during both wartime and peacetime. It is notable that more rigorous studies such as ours that are population-based efforts to identify incident cases of ALS do not find such an association, and less rigorous studies that have relied on death certificate ascertainment of ALS are the only studies that have identified a positive association between military service and ALS.

Parkinson's Disease Findings. We observed significant associations between several aspects of military service and the late life risk of developing PD, including service in the military at times of war, and among certain classes of military occupation. When compared to the men who had never served in the military and to men who served but not at times of war, men who were veterans of war had an 80% increased risk of PD. Deployment during World War II was associated with a doubling of PD risk, and deployment during Viet Nam War was associated with a 2.3-fold increased risk of PD. The only significant association observed for specific military occupation was for the class of workers engaged in electrical repair (adjusted OR 3.9, 95% CI 1.4-10.8; p=0.008). Our findings raise concerns that physical or chemical exposures during wartime military service could affect the risk of developing Parkinson's disease. As ours is the first study to investigate whether military service leads to an increased risk of Parkinson's disease, additional studies are needed to replicate these findings and to delve further into the possible reasons for the associations we observed.

Section I

Final Progress Report

Significant (Key) Findings

A sizable proportion (> 40%) of U.S. men who are currently at the age of risk for developing neurodegenerative diseases such as Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) have been deployed in previous U.S. military conflicts or have been employed by the military during peacetime, making it important to investigate a possible association of military service and these diseases in the current aging cohort. This topic is of particular relevance because of recent studies identifying military service as a risk factor for ALS, as well as a recent Institute of Medicine report that determined that there is limited and suggestive evidence of an association between herbicide exposure and later development of PD.

Parkinson's disease. We observed significant associations between several aspects of military service and the late life risk of developing Parkinson's disease, including service in the military at times of war, and among certain classes of military occupation. Deployment during World War II was associated with a doubling of PD risk, and deployment during Viet Nam War was associated with a 2.3-fold increased risk of PD. In contrast, deployment at the time of the Korean War was not associated with an increased risk of PD. Our findings raise concerns that physical or chemical exposures during wartime military service affect the risk of developing Parkinson's disease later in life. Given that a sizable proportion of U.S. men who are currently at the age for developing PD have been deployed during previous U.S. military conflicts, the potential public health significance is tremendous.

Amyotrophic lateral sclerosis. Although early studies suggested that military service in the first Persian Gulf War was associated with an increased risk of ALS or that military service in general increases the risk of developing ALS, in two rigorous population-based case-control studies of ALS, we found no evidence suggesting that military service influences the risk of ALS.

Translation of Findings

The focus of our investigations was on whether service in the military increases the risk of late-life neurodegenerative diseases, Parkinson's disease and amyotrophic lateral sclerosis. At this stage of investigation, we cannot yet indicate how our findings may be translated in order to prevent diseases or injuries that may occur as a result of military service, however, our findings can be used to guide future investigations (*see Impact of Findings below*).

Outcomes/Impact

1) Potential outcomes. Our studies provided critical evidence regarding the possible association of military service with late-life neurodegenerative diseases. We conducted population-based epidemiologic studies that are much more rigorous than previous studies that have been reported in the recent scientific literature. Our goal was to determine whether military service is a risk factor for developing either Parkinson's disease (PD) or amyotrophic lateral sclerosis (ALS).

The chronic health effects of exposures during past periods of active military service have become an issue of serious concern to veterans and to the public at large. Bullman et al. [1994] recommended the establishment of a "registry of military personnel" with exposures to agents that could potentially have serious long-term health risks. In the absence of such a registry or data system, we are left with simpler approaches such as those described in this proposal. For the more recent time era, the Department of Defense established the "Defense Medical Surveillance System" (DMSS), a relational database that documents the military and medical experiences of 7 million service members who have served in the armed forces since 1990 [Rubertone 2002]. While this a wonderful development, it will not bear fruit soon for the investigation of neurodegenerative diseases which have usual onset when individuals are 60 years and older.

Very few large military cohorts from earlier conflicts have been followed prospectively, therefore we recommended that case-control studies in community settings should be carried out, given that a large percentage of men currently in the age-at-risk categories for ALS and PD have served in the military. Such studies would ideally involve the rapid ascertainment of newly diagnosed patients with ALS and the collection of rigorous interview data on occupational history, residential history and exposures in military settings (when possible accompanied by objective exposure data). Furthermore, such studies permit a tighter control for putative confounding variables, such as lifetime occupational history and trauma. Such studies included information on military service and deployment, locations of service, duration of service, as well as job duties and tasks while in the military. Such studies would be more likely than prospective studies to lend themselves to the validation of self-reported military service information, because the study subjects themselves are available for questioning. Since virtually all investigators carrying out epidemiologic studies of ALS and PD are collecting a lifetime occupational and residence history; objective methods developed in this study could be used in the future to supplement existing data to get more specific about putative military exposures. Of critical importance is using standardized data collection instruments and exposure assessment methods across studies to lay the groundwork so that environmental and genetic data can be combined across research sites in the future. In response to this concern, we formed the ALS Consortium of Epidemiologic Studies (ACES) to serve as a methodological resource for epidemiologists who plan to conduct epidemiologic studies of ALS (see http://aces.stanford.edu/). Methods for standardized collection of epidemiologic data have been developed for many important domains, including military occupations and exposures, lifestyle factors (smoking, alcohol, physical activity), trauma, family history of neurodegenerative disease, anthropometric measures; history of chronic diseases and medication use; and residential and occupational history.

2) Intermediate Outcomes. None

3) End Outcomes: None

Section 2

Scientific Report

Background for the Project:

The primary objective of this project was to determine whether military service is associated with the risk of developing the late-life neurodegenerative diseases, Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). The specific aims of this project are: (i) to develop exposure assessment methodology for collecting objective information about military occupations and exposures, and (ii) to apply our methodology to determine whether military service is associated with ALS and PD in three recently completed population-based case-control studies conducted in Western Washington and Northern California. We examined the association between military service and the risk of developing PD using data from four recently completed community-based case-control studies of PD and ALS conducted in Northern California and Western Washington State.

Specific Aims:

(1) Develop an exposure assessment methodology for collecting information about military occupations and exposures that may be associated with neurodegenerative diseases.

(2) Apply the newly developed methodology from specific aim #1 to determine whether military service is associated with ALS or PD in three recently completed population-based case-control studies conducted in Western Washington and Northern California.

Methodology:

We addressed our study aims by combining and analyzing data from two community-based case-control studies of ALS (one from western Washington state (1990-1994) and the other from northern California (2000- 2004)), as well as two case-control studies of PD conducted in Northern California (1994-1995, 2000-2004). These datasets contains a total of 360 ALS cases, 584 PD cases, and 1376 age- and sex-matched control subjects. The risk factor questionnaire administered by trained interviewers was identical for the PEAK and GEM studies within KPNC, as Dr. Nelson was the principal investigator of both studies. Similarly, with very few differences, the interview used in the Western Washington study was identical to the risk factor questionnaire used in the PEAK and GEM studies, since Dr. Nelson developed the methodology for the Washington study at the time of her doctoral program in 1987-1991. Trained interviewers conducted structured in-person interviews to obtain risk factor data from all study subjects. The interviews included information on demographic characteristics; history of tobacco, alcohol, and caffeine consumption; anthropometric measures; history of chronic diseases and anti-inflammatory medication use; residential and occupational history; and family history of neurodegenerative disorders. Detailed information on all jobs held for at least one year was collected for the period from age 15 years to the reference date. For each job, subjects provided information on job title and industry, a detailed description of tasks performed, the year in which the job began and ended, and numbers of hours worked per week. Information collected during the interview pertained to exposures prior to an assigned "reference date." The reference date for cases was the date of diagnosis of ALS or PD. For each control in a given birth year and gender stratum, a reference date was randomly assigned

based on the distribution of reference dates among cases within that stratum. We constructed measures of military occupational and deployment exposure using objective data from each subject's structured interview, which includes extensive information on lifetime occupational and residential history, as well as military job titles and war-zone deployment data. Our studies collected information using the Standard Occupational Code and thus we needed to undertake a time-consuming process of translating each of those codes in the corresponding Military Occupational Code. The military occupational codes were then grouped into the following categories: (1) infantry/combat; (2) motor transport; (3) communications; (4) aircraft or vehicle maintenance; (5) engineer or construction facilities; (6) supply administration; (7) field artillery; and (9) other. We analyzed the data using multivariate unconditional logistic regression, with adjustment for age and other potential confounding variables that could influence the association between military employment and PD (cigarette smoking, caffeine consumption, alcohol intake, sociodemographic characteristics).

Results and Discussion:

Parkinson's Disease Studies. The strengths of the project included the availability of a large group of well-characterized men with Parkinson's disease and age-matched controls from the same underlying population, which is racially diverse and broadly representative of the underlying population in the San Francisco Bay area. Moreover, the availability of life- long occupational and residential histories for all men in this study, as well as extensive information on other risk factors for PD, enabled a very efficient and cost-effective opportunity to examine the association of military service with Parkinson's disease. This population includes not only lifelong information regarding location and duration of military service, but also detailed descriptions of jobs and job tasks performed during military service, as well as equally detailed residential and occupational information for all civilian jobs.

Because military service was rare among women (n=36 PD cases; n=36 controls), the investigation of military employment was restricted to male PD patients and male controls without PD. The frequency of military service was very high among men who were on average age 70 in 1994-95; 69% of men with Parkinson's disease and 64% of their age-matched controls had served in the military. When compared to the men who had never served in the military, men that served in the military during peacetime but never during a conflict, were not at increased risk of PD (adjusted odds ratio (OR) = 1.1, 95% confidence interval (CI) 0.7-1.5; p-NS). However, the risk of PD was significantly increased among men who were deployed during one or more wars (adjusted OR= 1.8, 95% CI 1.2-2.8; $p<0.01$). Interestingly, the risk of PD was increased among men who were deployed during World II (OR = 2.0, 95% CI 1.2-3.3, $p<0.005$), but not among men who served at the time of World War II who were not deployed) (OR = 1.0, 95% CI 0.7-1.6; p-NS). Similarly, the risk of PD was increased among men who were deployed during the Vietnam war (OR 2.3, 95% CI 0.9-6.2, $p<0.10$), but not among men who served at the time of the Vietnam War but were not deployed (OR = 1.0, 95% CI 0.5-1.7; p-NS). No increased risk of PD was observed among men who were in the military at the time of the Korean war, either among the deployed (OR = 1.7, 95% CI 0.9-3.2, p-NS) or the non-deployed (OR = 1.2, 95% CI 0.7-2.1; p-NS); however, there were relatively few men who served during that era and so the number of subjects was fewer than for other U.S. conflicts. Of note is that the associations between military deployment during wars and PD were not affected after statistical adjustment

for known factors associated with PD, including cigarette smoking, caffeine consumption, alcohol intake, education or socioeconomic status.

We examined the association of military specialty occupations in relation to PD risk, after carrying out a detailed classification and analysis of military job title according to class of occupation. We observed no association of PD with previous military occupations in the following categories: clerical (adjusted OR 1.2; 95% CI 0.8-1.8), communications (adjusted OR=1.0; 95% CI 0.5-2.0), supply management (adjusted OR 0.9; 95% CI 0.5-1.7), pilot (adjusted OR 0.9, 95% CI 0.4-2.0), vehicle mechanic (adjusted OR 1.0, 95% CI 0.6-1.6), motor transport (adjusted OR 0.9, 95% CI 0.5-1.8), combat (OR 1.0, 95% CI 0.5-2.1), or field artillery work (OR 1.2, 95% CI 0.6-2.2). A moderately increased but non-significant association was observed for individuals employed in construction or engineering positions (adjusted OR 1.5, 95% CI 0.8-2.6). The only significant association observed for specific military jobs was for the class of workers engaged in electrical repair (adjusted OR 3.9, 95% CI 1.4-10.8; p=0.008), which comprised 3.7% of male PD cases and 1.0% of male controls.

*Amyotrophic Lateral Sclerosis Studies.*_The combined sample size for the two studies of ALS was 339 incident ALS cases and 737 population controls (Western Washington State study: n=174 cases, 378 controls; Kaiser Northern California: n=165 cases, n=389 controls). The strengths of these studies include (i) the identification of incident cases of ALS according to standardized ALS diagnostic criteria, (ii) high quality detailed lifelong occupational, residential and lifestyle information including military and civilian occupations, and (iii) availability of information on other possible risk factors that could confound the associations of interest.

Study Findings Among Women. Military service was uncommon among women with ALS in our studies, occurring among 7-8% of women controls. There was no association of military service with ALS, either in the combined studies analysis (age-, sex- and study-adjusted OR=1.1; 95% CI 0.5-2.2; p=0.90; 8.1% of female cases versus 7.6% of female controls had prior military service), or within either the Western Washington State study (adjusted OR=0.7; 95% CI 0.2-2.3; p=0.57; 5.0% of female cases versus 7.0% of female controls), or within the Kaiser Northern California study (adjusted OR=1.4; 95% CI 0.5-3.6; p=0.50; 11.4% of female cases versus 8.3% of female controls had prior military service). The numbers of female cases and controls were too small for additional analyses according to wartime/peacetime or duration of service.

Study Findings Among Men. Prior military service was very common among men with ALS in our studies, occurring among 56% of male controls in both studies. There was no association of military service with ALS, either in the combined studies analysis (age-, sex- and study-adjusted OR=1.1; 95% CI 0.8-1.5; p=0.79; 57.4% of male cases versus 56.1% of male controls had prior military service), or within either the Western Washington State study (adjusted OR=1.2; 95% CI 0.7-2.0; p=0.61; 59.0% of male cases versus 55.8% of male controls), or within the Kaiser Northern California study (adjusted OR=1.0; 95% CI 0.6-1.6; p=0.90; 55.8% of male cases versus 56.5% of male controls had prior military service). No dose-response relation with increasing years of military service was observed for either study or in the combined analysis. Men who served only during wartime were not at an increased risk of ALS (adjusted OR= 1.0; 95% CI 0.7-1.5; p=0.97), nor were men who served during both wartime and peacetime (adjusted OR=1.0; 95% CI 0.4-2.1; p=0.92), however, men who served as career military (i.e., at both wartime and peacetime has a slightly elevated but not significantly increased risk of ALS (adjusted OR = 1.6; 95% CI 0.8-3.5; p=0.20) with 6.8% or male cases and 4.3% of male controls in this category.

Because no significant associations were observed between military service and ALS in either of our studies, we did not conduct detailed analyses according to job titles and job tasks.

Recent studies have suggested that military service increases the risk of developing ALS and this putative association has been the subject of recent scientific proceedings and an Institute of Medicine (IOM) report [IOM 2006]. The IOM concluded that there was "limited and suggestive evidence of an association between military service and later development of ALS," and recommended that further studies be conducted to address this important question. Our study adds to this growing literature, but failed to find associations between military service and the occurrence of ALS in our case-control studies in western Washington state and northern California, despite military service being a common feature of male cases and controls in both of our studies. Our findings contrast with two studies reporting a higher incidence of ALS among young servicemen who were deployed to the first Persian Gulf War than servicemen who were not deployed [Haley 2003, Horner 2003], and an association of military service with ALS among men who were participants in a prospective cohort study of the American Cancer Society (1.5-fold increased risk of ALS mortality; 95% CI 1.1-2.1) [Weisskopf 2005] . Neither our study nor the study by Weisskopf et al. [2005], however, observed a significant association of duration of military service with ALS.

Of note, however, is that our findings are consistent with those of several recent case-control studies, for which all but one found no association of military service with ALS. The exception was a case-control study based on death certificate data from 4,745 cases and 14,235 matched controls in Texas [White 2002], which reported significant association of veteran status and ALS/MND death among men (OR 2.3; 95% CI 1.3-3.9), but not among women (OR 1.1, 95% CI 0.8-1.7). In contrast, no other ALS case-control studies, including our two studies, have observed a positive association between military service and ALS [Fang et al. 2009; Qureshi et al. 2006; Binacci et al. 2009].

Conclusions:

Parkinson's disease. As ours is the first study to investigate whether military employment and/or deployment leads to an increased risk of Parkinson's disease, additional studies are needed to replicate these findings and to delve further into the possible reasons for the associations we observed. Our findings raise concerns that physical or chemical exposures during wartime military service could affect the risk of developing Parkinson's disease, however, the only specific military job class that was associated with an increased risk of PD was electrical repair, with a nearly 4-fold increased risk of PD. Additional objective information is needed regarding the reasons for the observed association between military service during wartime and the risk of developing PD, with a focus on identifying the aspect(s) of military service or exposures during military deployment that could increase the risk of developing this late-life neurodegenerative disease. We recommend that additional studies be conducted that focus on the collection of detailed military-specific lifetime occupational history in order to identify the specific job classes, duties and exposures that may be associated with increased risk of PD, as well as other factors that are potentially relevant to military service, including intensive physical activity, trauma, and transmissible agents.

Amyotrophic lateral sclerosis. In summary, although early studies suggested that military service in the first Persian Gulf War was associated with an increased risk of ALS, more recent

studies find no consistent associations of military service with the risk of ALS. It is notable that more rigorous studies such as ours that are population-based efforts to identify incident cases of ALS do not find such an association, and less rigorous studies that have relied on death certificate ascertainment of ALS are the only studies that have identified a positive association between military service and ALS. This raises the question of whether there could be a somewhat biased over ascertainment of military service members among those who are ascertained through death certificates.

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Publications:
We are in the process of preparing two manuscripts describing the study results, a brief communication for the ALS study findings, and a full-length submission for the PD study findings.

Inclusion of Children: No (N/A

Materials available for other investigators: None (N/A)

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Inclusion Enrollment Report			
Study Title:	Retrospective Assessment of Military Occupations & Neurodegenerative Diseases		
Total Enrollment:	983	**Protocol Number:**	19508
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PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

Ethnic Category	Females	Males	Sex/Gender Unknown or Not Reported	Total
Hispanic or Latino	2	32		34 **
Not Hispanic or Latino	105	844		949
Unknown (individuals not reporting ethnicity)				
Ethnic Category: Total of All Subjects*	107	876		983 *
Racial Categories				
American Indian/Alaska Native	6	36		42
Asian	5	34		39
Native Hawaiian or Other Pacific Islander	2	1		3
Black or African American	12	37		49
White	82	765		847
More Than One Race				
Unknown or Not Reported		3		3
Racial Categories: Total of All Subjects*	107	876		983 *

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

Racial Categories	Females	Males	Sex/Gender Unknown or Not Reported	Total
American Indian or Alaska Native	6	36		42
Asian	5	34		39
Native Hawaiian or Other Pacific Islander	2	1		**3**
Black or African American	12	37		49
White	80	733		813
More Than One Race				
Unknown or Not Reported				3
Racial Categories: Total of Hispanics or Latinos**	2	32		34 **

- These totals must agree. ** These totals must agree.