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ALS and the Military: A Population-Based Study in the Danish Registries

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Abstract

Background—Prior studies have suggested that military service may be associated with the development of amyotrophic lateral sclerosis. We conducted a population-based case-control study in Denmark to assess whether occupation in the Danish military is associated with an increased risk of developing amyotrophic lateral sclerosis.

Methods—There were 3,650 incident cases of amyotrophic lateral sclerosis recorded in the Danish National Patient Registry between 1982 and 2009. Each case was matched to 100 age- and sex-matched population controls alive and free of amyotrophic lateral sclerosis on the date of the case diagnosis. Comprehensive occupational history was obtained from the Danish Pension Fund database, which began in 1964.

Results—2.4% (n=8,922) of controls had a history of employment in the military prior to the index date. Military employees overall had an elevated rate of ALS (OR=1.3; 95% CI: 1.1-1.6). A ten-year increase in years employed by the military was associated with an odds ratio of 1.2 (95% CI: 1.0-1.4), and all quartiles of time employed were elevated. There was little suggestion of a pattern across calendar year of first employment, but there was some evidence that increasing age at first employment was associated with increased ALS rates. Rates were highest in the decade immediately following the end of employment (OR=1.6; 95% CI: 1.2-2.2).

Conclusions—In this large population-based case-control study, employment by the military is associated with increased rates of ALS. These findings are consistent with earlier findings that military service or employment may entail exposure to risk factors for ALS.

INTRODUCTION

The causes of amyotrophic lateral sclerosis (ALS) are largely unknown. Nearly a decade after the first Gulf War in 1990-1991, studies began to document an association between

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military service and risk of ALS.[1-4] Two studies of Gulf War veterans observed a near-doubling of ALS rates in young veterans who had been deployed in the Gulf[2,3], while the large Cancer Prevention Study II (CPS-II) found a 50% increase in self-reported veterans.[4] An analysis of the National Longitudinal Mortality Study (NLMS), a large representative sample of the non-institutionalized U.S. population, found a hazard ratio of 1.21 (95% CI: 0.97-1.50) for ALS among all veterans, and a ratio of 1.46 (95% CI: 1.13-1.88) among WWII veterans.[5] In the only non-U.S. study to date, the rate of ALS in French military service members (rate = 1.7/100,000 per year), was lower than that of the general population, but the study was limited by its small size (n=73 ALS patients) and by its case ascertainment, and elevated rates were observed in those aged 40-54.[6] A recent review of thirty articles and abstracts concluded that "although current literature suggests a positive association between military service and ALS/MND etiology, it is too limited to make definitive statements."[7]

Several factors may explain a causal relationship between military service and an increased risk of ALS. Exposures that are more common in military service-members and that have been tentatively associated with ALS include: insecticides[8,9], aerosolized lead[8,10], traumatic injury[11-13], viral infections[14,15], and intense physical activity[16,17].

In the present study we used Danish registry data covering 27 years of ALS diagnoses to perform the largest analysis to date on the link between military occupations and ALS risk; this is also the first study outside the U.S. performed in a population representative sample.

METHODS

Case Ascertainment

We obtained cases from the Danish National Patient Registry, using primary discharge diagnoses of 348.0 (ICD-8) or G12.2 (ICD-10). ICD-8 codes were used in Denmark through 1993, with ICD-10 thereafter. All hospital admissions nationwide are captured by the National Patient Registry, beginning on January 1, 1977.[18] In a validation sub-study of 173 ALS cases identified this way, we obtained medical records and confirmed the ALS diagnosis in 160 (92.5%).[19] We found no difference in predictive validity between ICD-8 and ICD-10 codes in our validation sub-study.[19] An earlier validation sub-study in Denmark found confirmed ALS in only 68% of hospital discharge-identified records, but was based on only 25 cases and was limited to ICD-10 ALS codes.[20]

We limited our case definition to first diagnoses on or after January 1, 1982, a five-year washout period to reduce the inclusion of prevalent cases. Case ascertainment was performed through December 31, 2009, and the index date was the first recorded hospitalization with ALS recorded as the primary discharge diagnosis.

Control Selection

We obtained controls from the Central Person Registry, which covers all residents in Denmark since 1968.[21] We selected 100 controls for each case, individually matched on sex, age in 1-year windows, and who were free of an ALS diagnosis in the Patient Registry as of the index date (risk-set sampling). All inhabitants of Denmark are assigned a unique 10-digit

Central Person number, which includes information on date of birth and sex, and can be used to link between multiple databases, including the Central Person Registry, Danish National Patient Registry, and the Danish Pension Fund (see below).

Covariates

In addition to the matching variables of age, sex, and calendar date, we obtained information on job title, spouse's job title, marital status, and area of residence on the index date from the Central Person Registry. Job title was classified into five groups as a proxy for socioeconomic status (SES): academics and managers (1), high salaried (2), low salaried (3), skilled workers (4) and unskilled workers (5). When both an individual and his or her spouse's job title category were reported, we used the higher SES category (lowest number) of the two. If neither was reported the individual's job title was considered missing, categorized using a missing indicator. Marriage status was categorized as married, unmarried, divorced, or widowed as of the index date. Area of residence was classified as Copenhagen/Aarhus/Odense (the three largest cities in Denmark), Other Denmark/Greenland, or Unknown.

Occupational History

We obtained employment histories from the Danish Pension Fund databases, which maintains employment data on all wage earners aged 16-66, beginning in 1964.[22] In the pension database each employment is recorded with start and end dates, the Central Person number of the employee, and a unique 8-digit company number determined by the tax authorities. The company number is based on its main activities as classified by Statistics Denmark, which employs an extended version of the International Standard Industrial Classification codes. For the present analysis we focused on: Air force, Marine, Army, Civil Defense, Home Guard, and the Royal Army, and Defense not elsewhere classified. The latter do not differentiate between Air force, Marine and Army. We calculated the total number of years employed by each branch. A record of employment by the Danish military in the pension database reflects only that the employee was paid by the military, a definition that may include both military and civilian employees. Military service in Denmark is compulsory for all men who meet a minimal level of overall health, and has been limited to less than one year since 1973 with some rare exceptions, e.g. the royal guard. Because pension records – and thus our ability to classify someone as employed by the military – begin only after one year of employment in the military, our exposure definition excludes those who only served their compulsory amount.

Our primary analysis consisted of whether or not an individual had ever worked in the military (or a particular branch) prior to the index date. We analyzed amount of time spent in each occupation by quartiles of time worked in each branch, and as a continuous number of years. For each job, we also determined the decade and the age during which the individual was first employed. Finally, we categorized the number of years between the index date and the last year of employment in the military.

Statistical Analysis

All models were fit via conditional logistic regression, with strata defined by the age-, sex-, and calendar year-matched sets. We categorized the year first employed in a particular occupation as: ≤1964, 1965-1974, 1975-1984, 1985-1994, and 1995-2009. Because recording of employment history began in 1964, any individual employed prior to 1964 and still employed at that time would be included in the ≤1964 category; the category is thus a combination of prevalent and incident "hires". We categorized the number of years employed in the military based on the distribution of number of years worked among cases: ≤1964, 1.0-2.4, 2.4-4.7, 4.7-12.4, ≥12.4. Results were unchanged when the quartiles were based on the distribution among controls. We were forced to use a category for ≤1964 because the age at which an individual was first employed prior to 1964 is unknown, only that they were employed at that time and potentially some amount of time earlier. We can therefore not accurately calculate the total number of years worked (or age first worked) for those individuals. We categorized the age at which an individual was first employed by the military as: ≤1964, <21, 21-29, and 30+. The category for ≤1964 was used for the reasons described above. We categorized the number of years between the year of last employment in the military and the index date as: 0-9, 10-19, 20-29, and 30+, with no military occupation serving as the reference category. We modeled number of years employed by the military and age at first military employment linear to assess trends. For years employed we used an indicator variable to identify those whose employment began before 1964 and set their time of employment as a fixed value, and for age at first military employment we used an indicator to identify those who never worked for the military, and set their age of first employment as a fixed value. This has the effect of only modeling the relationship among those with known or well-defined values, but without destroying the nature of the matched case-control study.

In addition to the matching factors, all models were adjusted for SES. Inclusion of area of residence as of the index date did not change the estimates for any of the exposures of interest, so we omitted residence from the final models. As a sensitivity analysis we further adjusted our analyses for time spent in the military; point estimates were largely unchanged. We assessed departures from linearity for continuous measures via penalized cubic splines in R, with the penalty chosen by Akaike Information Criteria.[23]

Finally, we employed a quantitative sensitivity analysis to assess the potential for a dichotomous confounder, such as smoking behavior, to explain our results.[24] We based the characteristics of the putative confounder on a previously published meta-analysis of the association between smoking and ALS,[25] and based confounder prevalence rates on available data on smoking in Denmark.[26]

This study was determined to be exempt by the Harvard School of Public Health IRB and was approved by the Danish Data Protection Agency. The analysis consisted solely of secondary analysis of existing data; therefore, informed consent was deemed unnecessary.

RESULTS

Between January 1, 1982 and December 31, 2009 there were 3,650 diagnosed cases of ALS in Denmark. Table 1 shows descriptive statistics for controls with and without a history of military occupations. Military employees were more likely to be male and were younger than non-military. The average year of birth among those with a history of military employment was 1940, while the average for those without was 1932. Military employees were also more likely to reside in the three large cities in Denmark, have higher SES, and be married than non-military.

Among controls, 2.4% (n=8,922) had a history of employment in the military prior to the index date. Military employees overall had an elevated rate of ALS diagnosis (OR=1.3; 95% CI: 1.1-1.6) (Table 2). There was little evidence of a difference by branch, though small numbers in the marines and army limit comparisons. Because there was a total of only one case with a history of Civil Defense, Home Guard, or Royal Guard occupation, we did not report results for these branches individually. There was little evidence of effect modification of military service (any branch) by sex; all sex-stratified measures were similar with broadly overlapping confidence intervals.

Table 3 shows the results for total number of years employed in the military. Quartiles were defined from cases with a history of post-1964 employment in the military. ALS rates were elevated for all quartiles, though sparse numbers resulted in wide confidence intervals. When the quartiles were further dichotomized into those who worked more or less than the 2.1 years (the first quartile cut-point), the odds of ALS in those who worked more than 2.1 years was 1.5 times the odds in those who worked less than 2.1 years (95% CI 1.1-1.9) (Data not shown). When modeled linearly, each ten-year increment in number of years worked (which roughly corresponds to the IQR in ever-employed cases; see Table 3) for the military was associated with an odds ratio of 1.2 (95% CI 1.0-1.4) (Data not shown). Visual inspection of flexible splines indicated no substantial departures from linearity or threshold effects.

The association did not vary much by year first worked in the military (Table 3), although decreasing numbers limited our ability to discern differences in more recent decades. We observed some evidence that military employment begun after the age of 21 was more highly associated with ALS than earlier service (Table 3). When modeled linearly however, each five-year increment in age-at-first-military-employment was associated with a null odds ratio of 1.0 (95% CI 0.97-1.1) (Data not shown). Further adjustment for number of years in the military, entered in quartiles, did not substantially change the point estimates.

When we categorized individuals by how long it had been since their last military employment, there was a suggestion that employment in the decade prior to the index was more strongly associated with ALS (Table 3). Military employment in the decade prior to the index date was associated an odds of ALS 1.6 times higher than those who did not work for the military (95% CI 1.2-2.2), whereas military employment in the decades more than a decade prior to the index date was associated odds ratios much closer to the null.

Sensitivity Analysis

We employed a sensitivity analysis to assess the potential for a single dichotomous exposure (smoking) to explain our results. A meta-analysis for the association between smoking and ALS reported a pooled rate ratio of 1.3.[25] With an estimated 30% of the population as ever-smokers in 2000, we varied the prevalence of smoking in those employed by the military to assess the stability of our results. Our best estimate of the smoking prevalence in the Danish military is 34% as reported in the survey of military personnel. This resulted in a biased OR of only 1.01. If the smoking prevalence in military employees was twice as high (60%) the OR would be 1.08. In order to get a biased OR as large as what we found in this paper (1.3), the odds ratio linking ALS and smoking would have to be as high as 1.6, which is considerably higher than the pooled estimate, particularly that for males, and smoking prevalence among Danish military employees would have to be 90%.

DISCUSSION

In our study, employment in the Danish military was associated with a 1.3-fold increased rate of ALS, with some evidence of a trend with increasing years of employment. Additionally, we found some evidence that Air Force and Marine employees were at a heightened risk for ALS, although given the numbers in the different categories, it is not clear whether a true difference by branch exists. There was no strong evidence for increased risk in any particular period of employment or age at first employment. Our current findings are the first outside the U.S. to use a population-representative sample and we find results similar to prior U.S.-based studies.

Five prior studies have assessed ALS risk in relation to military service. The first, in Gulf War veterans, reported a standardized mortality ratio of 2.27 (95% CI 1.27-3.88) for ALS diagnosed before the age of 45 in a three-year period from 1995 to 1998.[2] This study was based in a cohort of 695,000 United States service members who served in the region of the Gulf War between August 1990 and April 1991, with case ascertainment through a variety of methods, including informal ties, Department of Defense, Department of Veterans Affairs, and the ALS association registries. A second study compared deployed to non-deployed Gulf War era veterans, and similarly found roughly a doubling in risk of ALS (Rate Ratio=1.92; 95% CI 1.29-2.84).[3] A third study in the national CPS-II cohort of roughly 500,000 men found that a self-reported history of service (“Were you in the US Armed Services?”) in the US Armed Forces was associated with a risk ratio of 1.53 (95% CI 1.12-2.09).[4] A large study in a U.S.-representative sample of self-reported military service found a similar association to the current study.[5] Finally, a study of 73 French military service members with ALS found a slightly decreased rate of ALS in former service members overall as compared to the general population, although the study was limited by the fact that cases were limited to those still receiving military health care, creating the potential for downward selection bias. Despite this, elevated rates were observed in those aged 40-54.[6]

There is limited data on the exposures or conditions encountered with employment in the military in Denmark. Currently, A survey done by the Danish Cancer Society in 2004 on the risks associated with military radar equipment surveyed 1,125 men without cancer employed by the Danish military.[27] While the survey was conducted in a substantially younger cohort of military employees, the results indicated that roughly one third reported exposure within or outside the military to welding, metal processing, or organic solvents. Twenty-eight percent reported daily smoking, with a further 34% reporting a history of smoking. This is nearly the same as the overall reported smoking prevalence in Denmark of 30% in 2000 in those over the age of 15.[26] The prior U.S. studies of Gulf War veterans looked specifically at deployed veterans with the suggestion that some aspect of deployment accounts for the increased risk of ALS.[2,3,14,28] Only about one thousand Danish military service members per year have been deployed in recent decades, and the circumstances of those who are deployed are somewhat different than for U.S. military personnel. For example, deployed Danish military personnel rarely see combat prior to the war in former Yugoslavia in the 1990's. Thus, it seems unlikely that some aspect of deployment would account for our findings among Danish military workers.

A further analysis of the Gulf War veterans study found that the increased risk of ALS in deployed veterans had returned to that of non-deployed veterans with ten years after deployment.[28] We observed a similar pattern, although weaker. The first decade after employment was associated with the highest relative increase in ALS, although the rate of ALS remained elevated after a decade.

Occupation in the military may entail exposure to several factors that could explain a true association between military work and an increased risk of ALS. While few exposures have been definitely linked to ALS, some exposures that have been suggested to be linked to ALS and are more common in the military include: insecticides[8,9], aerosolized lead[8,10], traumatic injury[11-13], viral infections[14,15], and intense physical activity.[16,17] Military workers are also potentially exposed to organic solvents and formaldehyde, both of which have been suggested as linked to ALS.[27,29,30]

The present study is limited by the lack of military occupation history prior to 1964. In general, however, we would expect bias from this type of exposure misclassification to be towards the null, which could further explain the slightly lower effect estimates we observed in comparison with the U.S. studies. We were also unable to adjust for smoking, which is a suspected risk factor for ALS[31,32,25], although the evidence is weaker among men, who make up most of the Danish military employees[25,33]. However, Weisskopf et al. did not observe a change in their estimates when adjusting for smoking in the CPS-II study. Furthermore, unlike in the U.S., in Denmark smoking rates of military workers are comparable to those in the general population thus greatly reducing any possible confounding.[27] When we employed a quantitative sensitivity analysis, there was little evidence that realistic confounding by smoking could explain our observed results. Employment by the military in Denmark involves many activities in addition to traditional military services, but indirect data suggests that several suspected risk factors for ALS may be fairly common among the Danish military employees.[27]

A strength of this study is the structure of the healthcare system in Denmark. Prior findings in the U.S. may have been influenced by the fact that veterans in the U.S. were historically more likely to have access to healthcare, potentially leading to differential ALS ascertainment. Denmark has had universal healthcare coverage since the 1930s, greatly limiting the possibility that access to care is driving our findings.

Associations between military work and ALS have now been reproduced in multiple large studies of differing design. Future studies should focus on collecting more detailed information, particularly on potential confounders of smoking and physical activity, and on potential specific risk factors including what kind of military work is undertaken and what types of exposures are accrued. Such studies might be accomplished via prospective case-control studies with data collection from military databases.

In summary, we found evidence for a link between Danish military service and ALS risk in a large, population-based study. It is, to our knowledge, the first registry-based study using objective records of military employment and ALS diagnosis, and the first population-representative study outside of the U.S. Our findings underline the importance and value in working within military populations to identify specific risk factors that could account for the increased risk of ALS among military personnel.

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Table 1

Descriptive statistics of controls, Denmark January 1 1982 – December 31 2009, separated by ever having a history of military occupation. Characteristics describe the controls on the case (index) date.

	Military (n=8,922)	Non-Military (n=356,078)
Male sex, n (%)	7507 (84)	187893 (53)
Age (years), n (%)		
<45	970 (11)	19030 (5.3)
45-54	1723 (19)	40277 (11)
55-64	2860 (32)	89740 (25)
65-74	2351 (26)	122749 (35)
74-85	934 (11)	74766 (21)
≥85	84 (0.94)	9516 (2.7)
Residence, n (%)		
Copenhagen/Aarhus/Odense	4291 (48)	157758 (44)
Other Denmark/Greenland	4623 (52)	197130 (55)
Unknown	8 (0.09)	1190 (0.33)
SES*, n (%)		
1 – High	2141 (24)	33332 (9.4)
2	974 (11)	39353 (11)
3	1477 (17)	64518 (18)
4	2278 (26)	97102 (27)
5 – Low	1391 (16)	71584 (20)
Unknown	661 (7.4)	50189 (14)
Marriage Status, n (%)		
Married	6205 (70)	219082 (62)
Unmarried	827 (9.3)	32645 (9.2)
Divorced	1121 (13)	36755 (10)
Widower	769 (8.6)	67596 (19)

*SES: socioeconomic status

Table 2

Odds ratios for history of employment in the military (overall) and by branch.

Branch	Cases, n (%)	Controls, n (%)	OR*
No Military	3534 (97)	356078 (98)	ref
Any Military	116 (3.2)	8922 (2.4)	1.3 (1.1-1.6)
Air Force	24 (0.66)	1537 (0.42)	1.5 (1.0-2.3)
Marines	9 (0.25)	570 (0.16)	1.6 (0.84-3.2)
Army	10 (0.27)	1394 (0.38)	0.70 (0.37-1.3)
Defense NEC**	98 (2.7)	7261 (2.0)	1.3 (1.1-1.7)

*Adjusted for matching factors and socioeconomic status (SES)

**NEC = Not Elsewhere Classified

Table 3

Odds ratios by number of years in a military occupation.

Number of years employed by military*	**Case subjects, n (%)**	**Control subjects, n (%)**	**Odds ratio****
None	3534 (97)	356078 (98)	ref
Pre-1964***	49 (1.3)	3873 (1.1)	1.2 (0.93-1.6)
1st Quartile	16 (0.44)	1512 (0.41)	1.1 (0.65-1.8)
2nd Quartile	17 (0.47)	1126 (0.31)	1.5 (0.95-2.5)
3rd Quartile	17 (0.47)	1212 (0.33)	1.4 (0.89-2.3)
4th Quartile	17 (0.47)	1199 (0.33)	1.4 (0.87-2.3)
Calendar year of first employment by military			
None	3534 (97)	356078 (98)	ref
≤1964	49 (1.3)	3873 (1.1)	1.2 (0.93-1.7)
1965-1974	39 (1.1)	2797 (0.77)	1.4 (1.0-1.9)
1975-1984	18 (0.49)	1500 (0.41)	1.2 (0.76-2.0)
1985-1994	9 (0.25)	564 (0.15)	1.6 (0.83-3.2)
1995-2009	1 (0.03)	188 (0.05)	0.53 (0.07-3.8)
Age (years) at first employment by military			
None	3534 (97)	356078 (98)	ref
Pre-1964***	46 (1.3)	3415 (0.94)	1.3 (1.0-1.8)
<21	14 (0.38)	1812 (0.50)	0.78 (0.45-1.3)
21-29	33 (0.90)	2055 (0.56)	1.6 (1.1-2.3)
30+	23 (0.63)	1640 (0.45)	1.4 (0.94-2.1)
Number of years since final employment by military			
None	3534 (97)	356078 (98)	ref
0-9	46 (1.3)	2800 (0.77)	1.6 (1.2-2.2)
10-19	20 (0.55)	2186 (0.60)	0.91 (0.58-1.4)
20-29	27 (0.74)	2067 (0.57)	1.3 (0.89-1.9)
30+	23 (0.63)	1869 (0.51)	1.2 (0.82-1.9)

* Quartile cut points calculated from cases with non-zero employment: 2.1, 4.7, 12.4 years

** Adjusted for matching factors (age, sex, index date) and socioeconomic status

*** The number of years of employment and the age at first employment can only be definitively established for those who began work after 1964