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Opinion paper

Military service and the risk of amyotrophic lateral sclerosis: A meta-analysis

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ABSTRACT

To explore the relationship between the risk of amyotrophic lateral sclerosis and exposure to overall military service, we conducted a search of articles relevant to military service and the risk of ALS that used human subjects and were published in English through 20 May 2016, using Ovid Medline and Embase databases. Studies specially investigating the risk of ALS for Gulf war veterans were excluded. Quality of the cohort and case-control studies was assessed according to the Newcastle-Ottawa Scale (NOS). Analysis of data and publication bias were performed with Review Manager 5.3. A total of 8 case-control studies and 3 cohort studies were included in the meta-analysis. Only two case-control studies were conducted in Japan, comparing to 9 studies conducted in Europe/USA. The NOS scores of all studies were $\geq 6/9$. The risk of ALS was significantly increased in military personnel compared to non-military personnel (pooled OR = 1.29, 95% CI: 1.08–1.54, by random-effects model), with a moderate heterogeneity ($P = 0.01$, $I^2 = 55\%$) due to some studies with lower quality, conformed by subgroup and sensitivity analysis. The present meta-analysis supports a positive association between overall military service and the risk of ALS. Additional studies are needed to find out related factors influencing the ALS risk of veterans, especially by gender and for specific geographic regions such as Asia. That would also do some favor to explore the etiology and mechanism of ALS.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is an idiopathic, fatal neurodegenerative disease of human motor system [1]. ALS affects motor neurons in the brain, brainstem and spinal cord, resulting in progressive muscle weakness and atrophy. In the United Kingdom, the term motor neuron disease (MND) is used for ALS [2]. ALS is considered to be a multi-factorial disease involving both genetic and environmental factors. An association between military service and ALS was first reported in connection with the 1990–1991 Persian Gulf War. Four cohorts and seven studies on this topic were published between 2000 and 2009 [3–6]. In 3 of the cohorts, investigators reported an increased ALS incidence or mortality among US military veterans deployed to the Gulf War as compared with veterans deployed to other areas [3–5] but in 1 study they did not [6]. The US Institute of Medicine Committee has reviewed the scientific literature on ALS in veterans in 2006 [7] and updated it recently [8], and they concluded that there

was ‘limited and suggestive evidence of an association between military service and later development of ALS’. Since then, several new studies on this topic have been conducted. In the present study, meta-analysis was performed to investigate the relationship between military service and the risk of ALS. Here we do not concern the Gulf War deployment but overall military service. Studies investigating the risk of ALS for Gulf war veterans were excluded, because this special topic has been fully discussed elsewhere, and those studies mostly compared Gulf war veterans to non-Gulf war veterans but not non-military personnel. Furthermore, there may be subject overlaps among those studies.

2. Methods

2.1. Search strategy

We conducted a systemic search of articles that reported military service in ALS patients published up to 31 May 2016 using the Ovid Medline and Embase databases. The search terms included “amyotrophic lateral sclerosis or motor neuron disease or ALS or MND or Charcot disease or Lou Gehrig’s disease” and “military or military personnel or military service or military

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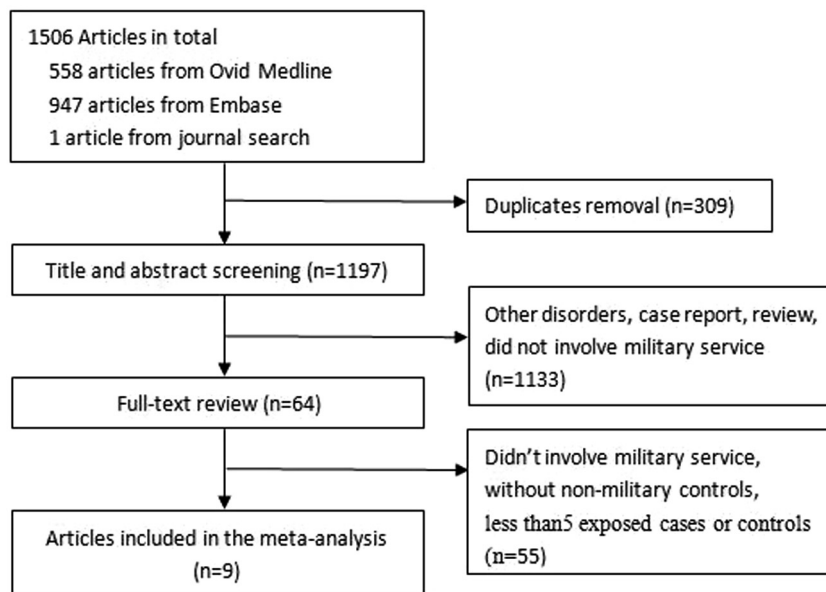


Fig. 1. The flow chart of the literature search in the meta-analysis.

deployment or military exposure or armed force or soldier or veteran or war or occupation". Both text and MeSH subject headings were used. We also reviewed the reference lists of relevant articles and retrieved reviews.

2.2. Inclusion criteria

To be included in the systematic review, studies had to meet the following criteria: (1) the study assessed the relationship between military service and ALS, (2) it was an observational study with a case-control or cohort design, (3) there was a comparison group of "healthy controls" (in case-control study) or non-military cohort (cohort study), and (4) the study reported an odds ratio (OR) or relative risk (RR) or hazard ratio (HR) and 95% CI, or the original data allowed this to be calculated. Articles were excluded if they were case reports, reviews, commentaries or non-human subjects were involved.

2.3. Data extraction and quality assessment

The quality of the included studies was evaluated using the Newcastle-Ottawa Quality (NOS) scale, a widely used tool for the quality assessment of observational/non-randomized studies [9]. The NOS scale assesses the selection of subjects, the comparability of study groups, and the ascertainment of either the exposure or outcome of interest with a total of 9 points.

For each study, following data was extracted: the first author's name, publication year, study design, area and period, number of participants, recruitment method, case ascertainment, control selection, assessment of exposure, matching and adjusted factors, and study results, i.e. OR, RR or HR and the corresponding 95% CI, and associated raw data for re-calculation or de novo estimation of missing measures by our team. Data extraction and quality assessment were performed independently by two investigators, and conflicts were resolved by a third party after discussion.

2.4. Statistical analysis

Analysis of association between military service and ALS was based on the adjusted OR and the 95% CI as reported by eligible studies. Since the absolute risk of ALS is low, the three measures

of association (OR, RR, and HR) are expected to yield similar estimates of OR. Meta-analysis was carried out using the Review Manager 5.3 software. Between-study heterogeneity was estimated by Q test and I^2 . If the Q test level $P < 0.10$, this was considered to indicate significant heterogeneity. If $I^2 > 50\%$, random-effects model was used to calculate the pooled OR, and fixed-effects model was employed when $I^2 < 50\%$. Funnel plots were used to evaluate possible publication bias. Subgroup analysis was conducted to minimize heterogeneity, which included analysis of study design, effect measurement, study quality, gender, geographic regions and ALS outcome. Sensitivity analysis was conducted to identify the stability of the results by omitting one study at a time and recalculating the OR on the remaining studies. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Included papers

A total of 1506 articles were retrieved. After removal of duplicate entries, 1197 articles remained and then underwent screening according to title and abstract, resulting in 1133 being excluded because (1) the study focused on disorders other than MND, or (2) it was not a cohort study or case-control study, or (3) the study did not involve military service. Another 51 articles were excluded after full-text review, including 10 articles assessing possible excess risk of ALS in Gulf War veterans compared to veterans who did not deploy to the Gulf War. 4 case-control studies were excluded because they did not have at least 5 exposed cases or controls [10–13]. Eventually, 9 articles remained were eligible for the meta-analysis (Fig. 1) [14–22]. The article was comprised of two independent case-control studies by Kondo et al. [14]. One conference abstract not yet published as original article [15] was also included. It provided separate results for men and women, with insufficient original data to calculate the OR value for the samples as a whole. We considered them as separate studies since they found different results by gender. According to the nine-point Newcastle-Ottawa Scale, all studies were of moderate to high quality (no less than 6 points). The details of each study are provided in Table 1.

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