Smoking and the risk of amyotrophic lateral sclerosis: a systematic review and meta-analysis

Alvaro Alonso,1,2 Giancarlo Logroscino,3 Miguel A Hernán4,5

ABSTRACT
Background Epidemiologic studies have provided inconsistent results on the association of cigarette smoking with the incidence of amyotrophic lateral sclerosis (ALS). To summarise published evidence and explore sources of heterogeneity, we conducted a systematic review and meta-analysis of studies that evaluated this association.

Methods Published studies evaluating the association of smoking with incidence of ALS were searched in bibliographic databases, with relevant information collected from each article. A random effects approach was used to pool the relative rate (RR) estimates from different studies. Between study heterogeneity was explored with a meta-regression approach.

Results 18 publications reported associations between smoking and ALS risk in 15 case control studies and five cohort studies. The pooled RR (95% CI) of ALS was 1.28 (0.97 to 1.68) for current versus never smokers and 1.12 (0.98 to 1.27) for ever versus never smokers. The study specifics RRs were heterogeneous (p<0.01). The proportion of women in the study population explained 46% of between study variability. The estimated RR (95% CI) of ALS for ever versus never smokers was 0.86 (0.71 to 1.03) in men and 1.66 (1.31 to 2.10) in women.

Interpretation This meta-analysis does not support an overall strong association of smoking with ALS risk but suggests that smoking might be associated with a higher risk of ALS in women.

INTRODUCTION
Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disease of unknown aetiology.1 Cigarette smoking has been proposed as a potential causative factor for ALS but published epidemiologic studies have provided inconsistent results. Methodological differences and heterogeneity in studied populations could account in part for these disparities.2

We conducted a systematic review and meta-analysis of published studies to estimate more precisely the association between smoking and incidence of ALS, and to identify sources of heterogeneity across studies.

METHODS
Search strategy
We performed a systematic search of published studies in Medline (1950—April 2009), EMBASE (1980—April 2009) and ISI Web of Science (1975—April 2009) using the terms ‘(ALS OR amyotrophic lateral sclerosis OR motor neuron disease) AND (smok*OR tobacco OR cigar*)’. We considered studies published in any language. Bibliographic references in the publications meeting inclusion criteria (see below) were reviewed to identify additional relevant papers.

Selection criteria
Studies meeting the following criteria were included in the review: (1) case control or cohort design; (2) information on smoking status referred to the period prior to diagnosis of ALS; (3) outcome defined as a medical diagnosis of ALS or presence of ALS in a death certificate; and (4) reporting of measures of association between smoking and ALS, or enough information to compute the association, or the corresponding author providing the necessary information on request. No specific exclusion criteria were applied.

Data extraction
From each identified eligible publication, the following information was abstracted: study design (case control, cohort), location, number of participants, period of recruitment, type of cases and controls (for case control studies), average follow-up (for cohort studies), method of case ascertainment, diagnostic criteria, response rate, mean age and range, proportion of men in the study sample, adjustment variables, as well as the main results (ORs or rate ratios of ALS in current smokers vs never smokers, in ever smokers vs never smokers and results by gender if available). In cases where the original publication did not provide enough information to estimate associations between smoking and ALS, the corresponding author was contacted.3–5

Statistical analysis
In case control studies with density sampling of controls, the OR estimates the rate ratio in the source population while in case control studies not using density sampling the OR is a good approximation to the rate ratio when incidence of disease is low, as in the case of ALS.6 Therefore, in this article we use the term rate ratio (RR) for association measures from both cohort and case control studies.

Heterogeneity of study specific RR estimates was evaluated by computing the Q and I2 statistics.7 I2 is a measure of heterogeneity recommended by the Cochrane collaboration, ranging between 0% (no heterogeneity) to 100%.7 Because of the evidence of heterogeneity, we did not adopt a fixed effects approach to pool the study specific estimates. Rather, we used the DerSimonian and Laird random effects method.8

To assess sources of heterogeneity we regressed the log RR on study specific characteristics

Table 1  Selected characteristics of studies included in the systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Case control studies</th>
<th>First author, year of publication</th>
<th>Location</th>
<th>Participants (cases/controls)</th>
<th>Period of recruitment</th>
<th>Type of cases</th>
<th>Controls</th>
<th>Case ascertainment</th>
<th>Diagnostic criteria</th>
<th>Response rate (% cases/controls)</th>
<th>Age (years) (mean [range])</th>
<th>% Men</th>
<th>Adjustment variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pierce-Ruhland, 1981</td>
<td>Houston, TX, USA</td>
<td>80/78</td>
<td>NS</td>
<td>Prevalent</td>
<td>Friends</td>
<td>Neurology clinic</td>
<td>Ad hoc</td>
<td>91/NS</td>
<td>52 (NS)</td>
<td>66</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Granieri, 1988</td>
<td>Ferrara, Italy</td>
<td>72/212</td>
<td>1982</td>
<td>Prevalent</td>
<td>Hospital</td>
<td>Neurology clinic</td>
<td>Ad hoc</td>
<td>NS</td>
<td>NS</td>
<td>61</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Provinciali, 1990</td>
<td>Ancona, Italy</td>
<td>77/80</td>
<td>1979–1987</td>
<td>Prevalent</td>
<td>Other neurological diseases</td>
<td>Neurology clinic</td>
<td>Ad hoc</td>
<td>NS</td>
<td>58 (NS)</td>
<td>74</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Savetierli, 1991</td>
<td>Palermo, Italy</td>
<td>46/92</td>
<td>NS</td>
<td>Prevalent</td>
<td>Friends/neighbours</td>
<td>Neurology clinic</td>
<td>Ad hoc</td>
<td>NS</td>
<td>NS</td>
<td>54</td>
<td>Age, sex, region, SES</td>
<td></td>
</tr>
<tr>
<td>Chancellor, 1993</td>
<td>Scotland</td>
<td>103/103</td>
<td>1990–1991</td>
<td>Prevalent</td>
<td>Community</td>
<td>ALS register</td>
<td>Ad hoc</td>
<td>70/NS</td>
<td>65 (35–96)</td>
<td>59</td>
<td>Age, sex, region</td>
<td></td>
</tr>
<tr>
<td>Kamel, 1999</td>
<td>Boston, MA, USA</td>
<td>110/256</td>
<td>1993–1996</td>
<td>Incident</td>
<td>Community</td>
<td>ALS clinic</td>
<td>Ad hoc</td>
<td>71/76</td>
<td>56 (30–80)</td>
<td>61</td>
<td>Age, sex, region, education</td>
<td></td>
</tr>
<tr>
<td>Qureshi, 2006</td>
<td>Boston, MA, USA</td>
<td>95/106</td>
<td>1998–2002</td>
<td>Prevalent</td>
<td>Friends/relatives</td>
<td>ALS clinic</td>
<td>EEC</td>
<td>NS</td>
<td>54 (NS)</td>
<td>63</td>
<td>Age, sex</td>
<td></td>
</tr>
<tr>
<td>Schmidt, 2008</td>
<td>USA</td>
<td>204/410</td>
<td>2003–2007</td>
<td>Incident</td>
<td>US Army veterans</td>
<td>US army veterans</td>
<td>EEC</td>
<td>85/30</td>
<td>62 (NS)</td>
<td>95</td>
<td>Age, sex, race, education</td>
<td></td>
</tr>
<tr>
<td>Okamoto, 2009</td>
<td>Tokai, Japan</td>
<td>153/306</td>
<td>2000–2005</td>
<td>Prevalent</td>
<td>Community</td>
<td>Neurology clinics</td>
<td>EEC</td>
<td>56/42</td>
<td>64 (NS)</td>
<td>60</td>
<td>Age, sex, physical activity, diet, trauma</td>
<td></td>
</tr>
<tr>
<td>Binanzi, 2009</td>
<td>Rome, Italy</td>
<td>77/185</td>
<td>2005–2006</td>
<td>Prevalent</td>
<td>Community</td>
<td>Neurology clinics</td>
<td>rEEC</td>
<td>NS</td>
<td>58 (28–84)</td>
<td>37</td>
<td>Age, sex</td>
<td></td>
</tr>
</tbody>
</table>

Cohort studies

<table>
<thead>
<tr>
<th>First author, year of publication</th>
<th>Location</th>
<th>Participants (cases/size)</th>
<th>Period of recruitment</th>
<th>Average follow-up</th>
<th>Case ascertainment</th>
<th>Diagnostic criteria</th>
<th>Retention rate (mean [range])</th>
<th>% Men</th>
<th>Adjustment variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weisskopf, women, 2004</td>
<td>USA</td>
<td>291/638 849</td>
<td>1982</td>
<td>10 years</td>
<td>NDI</td>
<td>NA</td>
<td>100%</td>
<td>56 (NS)</td>
<td>0</td>
</tr>
<tr>
<td>Weisskopf, men, 2004</td>
<td>USA</td>
<td>330/459 360</td>
<td>1982</td>
<td>10 years</td>
<td>NDI</td>
<td>NA</td>
<td>100%</td>
<td>56 (NS)</td>
<td>100</td>
</tr>
<tr>
<td>Fang, 2006</td>
<td>Sweden</td>
<td>160/280 558</td>
<td>1978–1993</td>
<td>19.5 years</td>
<td>NDI</td>
<td>NA</td>
<td>100%</td>
<td>56 (NS)</td>
<td>100</td>
</tr>
<tr>
<td>Wang, 2009</td>
<td>USA</td>
<td>633/1 130 644</td>
<td>NS</td>
<td>NS</td>
<td>NDI/self-report</td>
<td>NS</td>
<td>NS</td>
<td>51</td>
<td>Multivariate (NS)</td>
</tr>
<tr>
<td>Gallo, 2009</td>
<td>Europe</td>
<td>116/505 355</td>
<td>1991–2001</td>
<td>8.9 years</td>
<td>Death certificates</td>
<td>NA</td>
<td>NS</td>
<td>51</td>
<td>42</td>
</tr>
</tbody>
</table>

ALS, amyotrophic lateral sclerosis; EEC, El Escorial Criteria; NA, not applicable; NDI, US National Death Index; NS, not specified; rEEC, revised El Escorial Criteria (Airlie House Criteria); SES, socioeconomic status.
(percentage of men in the study population, average age of participants, study design and type of case—prevalent, incident or ALS death). Each study was weighted by the inverse of the study specific variance. This meta-regression model was fit separately by study design (case control vs cohort) and also in the entire sample of studies. Publication bias was assessed visually with a funnel plot.

RESULTS
The search identified 96 publications in Medline, 49 in EMBASE and 153 in ISI Web of Science. Sixteen publications met the inclusion criteria. Additionally, we included two conference abstracts not yet published as original articles. Fourteen references corresponded to case control studies (one of them included results from two different studies) and four to prospective cohorts. One of the cohorts provided separate results for men and women. We considered them as separate studies since they found different results by gender. Table 1 reports the main characteristics for studies included in the meta-analysis.

Seven case control studies and five cohorts provided associations comparing the risk of ALS in current smokers versus never smokers (figure 1). There was evidence of between study heterogeneity (case control studies: $Q=14.54$, $p=0.02$, $I^2=59%$; cohort studies: $Q=25.62$, $p<0.001$, $I^2=84%$; pooled results: $Q=41.76$, $p<0.001$, $I^2=74%$). The pooled RR and 95% CI of ALS in current smokers versus never smokers was $1.42$ ($0.96$ to $2.11$) in case control studies and $1.16$ ($0.78$ to $1.73$) in cohort studies. The pooled RR (95% CI) including case control and cohort studies was $1.28$ ($0.97$ to $1.68$).

Fifteen case control studies and five cohorts compared the risk of ALS in ever smokers versus never smokers (figure 1). No association was evident in cohort (pooled RR $1.13$, 95% CI $0.86$ to $1.49$) or in case control studies (pooled RR $1.09$, 95% CI $0.95$ to $1.26$). The pooled RR (95% CI) for cohort and case control studies was $1.12$ ($0.98$, $1.27$). There was substantial evidence of between study heterogeneity ($Q=44.74$, $p<0.001$, $I^2=58%$ for pooled case control and cohort studies).

A few studies evaluated the existence of a dose—response trend in the association between smoking and risk of ALS. Four of them reported evidence of a trend in the association between smoking amount and risk of ALS. Other studies, though, did not find any clear dose—response associations. The amount of information was insufficient to conduct a meta-regression analysis of dose—response.

We tested whether study specific characteristics contributed to explain the heterogeneity across studies. In a meta-regression model, the proportion of women was the only major predictor of the association between smoking and ALS incidence: a 10% increase in the proportion of women was significantly associated with an increase of 7% (95% CI 3% to 11%) in the RR between ever smoking and ALS. The proportion of women explained 46% of the total variability in the log RR. The meta-regression predicted an RR of ALS for ever smokers versus never smokers of $0.86$ (95% CI $0.71$, $1.05$) in men and $1.66$ (95% CI $1.51$, $2.10$) in women (see web figure 1, available online). Mean age of the study participants was weakly associated with the study specific risk ratios. The study specific RR of the association between ever smoking and ALS increased 5% (95% CI $-12%$ to $27%$) per each 5 year increase in the average age of study participants. Other variables, such as study design or type of case (prevalent, incident, mortality) did not explain substantial between study heterogeneity (see web table 1, available online). A funnel plot of studies that estimated the association for ever versus never smokers did not indicate publication bias (web figure 2, available online).

![Figure 1](http://jnnp.bmj.com/)

**Figure 1** Study specific and pooled rate ratios of smoking (current smokers vs never smokers; ever smokers vs never smokers) and amyotrophic lateral sclerosis in published case control and cohort studies.
DISCUSSION
This meta-analysis does not support an overall strong association of smoking with ALS risk but suggests that smoking might be associated with a higher risk of ALS in women.

Smoking could increase the risk of ALS through several mechanisms. Cigarette smoke contains a large amount of oxidant compounds which target certain molecules such as fatty acids in cell membranes and reduces the antioxidant capacity of the organism. For example, 8-hydroxy-2'-deoxyguanosine, a well established marker of oxidative damage to DNA, is increased in smokers compared with non-smokers, and its levels were higher in patients with sporadic ALS than in controls. Also, numerous chemicals, some of them with potential neurotoxic effects, are bound in cigarette smoke. Lead and formaldehyde, both present in cigarette smoke, have been associated with the risk of ALS in some studies.

The stronger association between smoking and ALS in women could be explained by differences in the metabolism of chemicals present in cigarette smoke. Many smoke components are metabolised by oxidation followed by conjugation. Some studies have shown that oxidation, but not conjugation, is upregulated in women, which leads to the accumulation of intermediate metabolites and increased oxidative stress. The association between smoking and other health outcomes, including thyroid disease, lung function and multiple sclerosis, is modified by sex.

The present meta-analysis has some limitations. The methodological quality of the included studies was not uniform. Some studies had an unclear definition of the outcome, potentially biased selection of controls, greater opportunities for measurement error in smoking assessment and insufficient control for confounding. However, methodological quality is unlikely to explain our findings as the results did not differ between cohort and case control studies even though cohort studies were of better methodological quality overall. As in any meta-analysis, publication bias could be present but there is no clear evidence of it.

We recommend that future studies on smoking and ALS provide sex specific estimates of the association while recognizing that stratified analysis of any individual study will have limited statistical power (see supplemental data, available online).

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Competing interests None.

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REFERENCES
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