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 3

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

#### Case control studies

<table>
<thead>
<tr>
<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&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Houston, TX, USA</td>
<td>80/78 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>Kondo-I, 1981&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Japan</td>
<td>712/367 1965–1966</td>
<td>Deaths</td>
<td>Spouses</td>
<td>Mortality registry</td>
<td>NA</td>
<td>76/NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Kondo-II, 1981&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Japan</td>
<td>158/158 1973</td>
<td>Prevalent</td>
<td>Community/hospital</td>
<td>Neurology clinic</td>
<td>Ad hoc</td>
<td>NS</td>
<td>66</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granieri, 1988&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Ferrara, Italy</td>
<td>72/212 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&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Ancona, Italy</td>
<td>77/80 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>Savettieri, 1991&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Palermo, Italy</td>
<td>46/92 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 Age, sex, region, SES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chancellor, 1993&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Scotland</td>
<td>103/103 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 Age, sex, region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinceti, 1997&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Reggio Emilia, Italy</td>
<td>16/39 NS</td>
<td>Prevalent</td>
<td>Community</td>
<td>ALS clinic</td>
<td>EEC</td>
<td>NS</td>
<td>65 (NS)</td>
<td>NS Age, sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kamel, 1998&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Boston, MA, USA</td>
<td>110/256 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 Age, sex, region, education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson, 2000&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Washington State, USA</td>
<td>161/321 1990–1994</td>
<td>Incident</td>
<td>Community</td>
<td>Multiple sources</td>
<td>Ad hoc</td>
<td>97/79</td>
<td>61 (NS)</td>
<td>55 Age, sex, education, alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qureshi, 2006&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Boston, MA, USA</td>
<td>95/106 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 Age, sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt, 2008&lt;sup&gt;34&lt;/sup&gt;</td>
<td>USA</td>
<td>204/410 2003–2007</td>
<td>Incident</td>
<td>US Army veterans</td>
<td>US army veterans ALs registry</td>
<td>EEC</td>
<td>85/30</td>
<td>62 (NS)</td>
<td>95 Age, sex, race, education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okamoto, 2009&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Tokai, Japan</td>
<td>153/306 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 Age, sex, physical activity, diet, trauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binazzi, 2009&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Rome, Italy</td>
<td>77/185 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 Age, sex</td>
<td></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</th>
<th>Age at baseline (mean (range))</th>
<th>% Men</th>
<th>Adjustment variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weisskopf, women, 2004&lt;sup&gt;18&lt;/sup&gt;</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 Age, alcohol, education</td>
<td></td>
</tr>
<tr>
<td>Weisskopf, men, 2004&lt;sup&gt;18&lt;/sup&gt;</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 Age, alcohol, education</td>
<td></td>
</tr>
<tr>
<td>Fang, 2006&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Sweden</td>
<td>160/280 558</td>
<td>1978–1993</td>
<td>19.5 years</td>
<td>Inpatient register</td>
<td>NA</td>
<td>100%</td>
<td>41 (NS)</td>
<td>100 Age, area of residence</td>
<td></td>
</tr>
<tr>
<td>Wang, 2009&lt;sup&gt;23&lt;/sup&gt;</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 Multivariate (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallo, 2009&lt;sup&gt;21&lt;/sup&gt;</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 (NS)</td>
<td>42 Age, sex, education, study centre</td>
<td></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.
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 within the association 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 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, abound 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 description 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 stratiﬁcation of analysis by individual study will have limited statistical power (see supplemental data, available online).

Acknowledgements The authors thank Andrew Chancellor, Enrico Granieri and Silke Schmidt who kindly provided additional unpublished information from some of the studies included in the meta-analysis.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES
Information for patients from JNNP

Study explores link between motor neurone disease and smoking

Smoking tobacco may increase the risk of a type of motor neurone disease, but only for women, a new study says.

What do we know already?

Amyotrophic lateral sclerosis (also known as ALS, and sometimes called Lou Gehrig disease) is a type of motor neurone disease. The nerve cells affecting movement die, making movement hard to control, and eventually impossible. The condition gets worse over time and is usually fatal within a few years. Doctors don’t know what causes amyotrophic lateral sclerosis. It runs in some families, suggesting there may be a genetic link, but 95 per cent of people with ALS have no family history of the illness. Cigarette smoking has been considered as a potential cause. But studies looking for a link between smoking and ALS so far have not shown clear results. Now researchers have combined the results of previous research, to see whether this gave a clearer picture.

What does the new study say?

There was no difference in risk of ALS between people who had ever smoked, never smoked, or were current or previous smokers. However, the study results varied a lot. When the researchers looked more closely at the results, they found that the number of women in the study explained a lot of this variation. So the researchers split the findings by men and women. They found no increase in risk of ALS for male smokers, but about a 60 per cent increase in risk for women who had smoked.
How reliable are the findings?
This type of study can’t show for certain that smoking does or doesn’t cause ALS. But it can show if there’s a strong link between smoking and risk of ALS. In this case, the overall figures don’t support a strong link, but it may be that the risk only applies to women.

What does this mean for me?
While smoking may not be the cause of ALS, we know for certain that it causes plenty of other serious health problems, such as many types of cancer, heart disease, and lung disease. This study doesn’t change the message that smoking damages health, and that giving up smoking is the best thing you can do for your health.

What should I do now?
If you want to give up smoking, speak to your health care provider.