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

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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 I^2 statistics.[7] I^2 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

Case control studies

First author, year of publication	Location	Participants (cases/ controls)	Period of recruitment	Type of cases	Controls	Case ascertainment	Diagnostic criteria	Response rate (%) cases/controls	Age (years) (mean (range))	% Men	Adjustment variables
Pierce-Ruhland, 1981[9]	Houston, TX, USA	80/78	NS	Prevalent	Friends	Neurology clinic	Ad hoc	91/NS	52 (NS)	66	NS
Kondo-I, 1981[10]	Japan	712/367	1965–1966	Deaths	Spouses	Mortality registry	NA	76/NS	NS	NS	NS
Kondo-II, 1981[10]	Japan	158/158	1973	Prevalent	Community/hospital	Neurology clinic	Ad hoc	NS	NS	66	NS
Granieri, 1988[3]	Ferrara, Italy	72/212	1982	Prevalent	Hospital	Neurology clinic	Ad hoc	NS	NS	61	NS
Provinciali, 1990[11]	Ancona, Italy	77/80	1979–1987	Prevalent	Other neurological diseases	Neurology clinic	Ad hoc	NS	58 (NS)	74	NS
Savettieri, 1991[12]	Palermo, Italy	46/92	NS	Prevalent	Friends/neighbours	Neurology clinic	Ad hoc	NS	NS	54	Age, sex, region, SES
Chancellor, 1993[4]	Scotland	103/103	1990–1991	Prevalent	Community	ALS register	Ad hoc	70/NS	65 (35–96)	59	Age, sex, region
Vinceti, 1997[13]	Reggio Emilia, Italy	16/39	NS	Prevalent	Community	ALS clinic	EEC	NS	65 (NS)	NS	Age, sex
Kamel, 1999[14]	Boston, MA, USA	110/256	1993–1996	Incident	Community	ALS clinic	Ad hoc	71/76	56 (30–80)	61	Age, sex, region, education
Nelson, 2000[15]	Washington State, USA	161/321	1990–1994	Incident	Community	Multiple sources	Ad hoc	97/79	61 (NS)	55	Age, sex, education, alcohol
Qureshi, 2006[16]	Boston, MA, USA	95/106	1998–2002	Prevalent	Friends/relatives	ALS clinic	EEC	NS	54 (NS)	63	Age, sex
Sutedja, 2007[17]	Utrecht, The Netherlands	364/392	2001–2005	Incident	Friends	ALS clinic	EEC	76/79	60 (24–83)	63	Education, occupation, age
Schmidt, 2008[5 34]	USA	204/410	2003–2007	Incident	US Army veterans	US army veterans ALS registry	EEC	85/30	62 (NS)	95	Age, sex, race, education
Okamoto, 2009[20]	Tokai, Japan	153/306	2000–2005	Prevalent	Community	Neurology clinics	EEC	56/42	64 (NS)	60	Age, sex, physical activity, diet, trauma
Binazzi, 2009[22]	Rome, Italy	77/185	2005–2006	Prevalent	Community	Neurology clinics	rEEC	NS	58 (28–84)	37	Age, sex

Cohort studies

First author, year of publication	Location	Participants (cases/cohort size)	Period of recruitment	Average follow-up	Case ascertainment	Diagnostic criteria	Retention rate	Age at baseline (mean (range))	% Men	Adjustment variables
Weisskopf, women, 2004[18]	USA	291/638 849	1982	10 years	NDI	NA	100%	56 (NS)	0	Age, alcohol, education
Weisskopf, men, 2004[18]	USA	330/459 360	1982	10 years	NDI	NA	100%	56 (NS)	100	Age, alcohol, education
Fang, 2006[19]	Sweden	160/280 558	1978–1993	19.6 years	Inpatient register	NS	100%	41 (NS)	100	Age, area of residence
Wang, 2008[23]	USA	633/1 130 644	NS	NS	NDI/self-report	NS	NS	NS	51	Multivariate (NS)
Gallo, 2009[21]	Europe	116/505 355	1991–2001	8.9 years	Death certificates	NA	NS	51 (NS)	42	Age, sex, education, study centre

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.[3 4 9–22] Additionally, we included two conference abstracts not yet published as original articles.[5 23] Fourteen references corresponded to case control studies (one of them included results from two different studies)[10] and four to prospective cohorts. One of the cohorts provided separate results for men and women.[18] 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.[14 15 21 23] Other studies, though, did not find any clear dose–response associations.[5 17–19] 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, 1.03) in men and 1.66 (95% CI 1.31, 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).

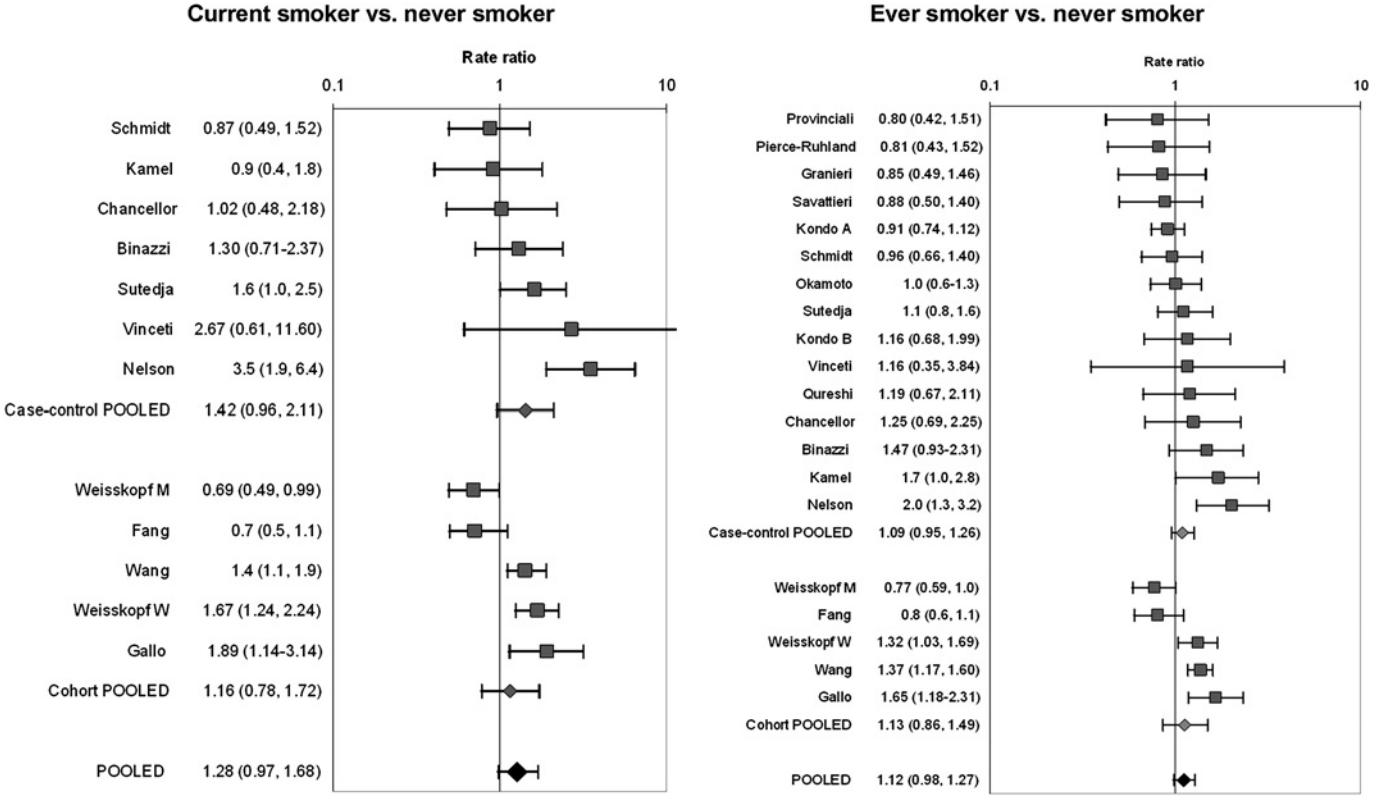

Figure 1 Study specific and pooled rate ratios of smoking (current smokers vs never smokers; ever smokers vs never smokers) and amyotrophic lateral sclerosis in published case control and cohort studies.

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.[24] For example, 8-hydroxy-2′-deoxyguanosine, a well established marker of oxidative damage to DNA, is increased in smokers compared with non-smokers,[25] and its levels were higher in patients with sporadic ALS than in controls.[26 27] 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.[28 29]

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.[30] The association between smoking and other health outcomes, including thyroid disease, lung function and multiple sclerosis, is modified by sex.[31–33]

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 recognising 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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