

2.	[6]	<p>Case-control study Incident cases of definite, probable or possible (WFN criteria) sporadic ALS, 1 year period 2001-2002, at the University Hospitals in Amsterdam and Utrecht: 280 patients sent a questionnaire <u>Primary outcome variable for the study:</u> Physical activity. (Results not discussed in this review) <u>Cases:</u> 219 (78%) patients who returned questionnaires. 61 non-respondents did not differ significantly from respondents on demographic and clinical data. <u>Controls:</u> 254 controls. Not spouse/ partner; preferably within 5 years of patient's age and same gender. 2 per patient requested – 58% obtained. <u>Period of observation:</u> Birth till one year before onset of clinical symptoms for patients; birth will completion of questionnaire for controls. <u>Smoking:</u> Determined as never, ever or current (for patients = in the year before clinical disease onset.), and used as a covariate in the logistic regression model.</p>	<p>“Smoking [and alcohol use] were the only factors in this logistic regression model that were independently associated with ALS (current smoking OR = 1.8, 95% CI 1.0 to 3.0, p=0.03).” (Data for alcohol nor shown).</p> <p><u>Primary smoking data:</u></p> <table border="1" data-bbox="1083 391 1580 613"> <thead> <tr> <th></th> <th>Patients N=219</th> <th>Controls N=254</th> </tr> </thead> <tbody> <tr> <td>Never</td> <td>74 (34%)</td> <td>100 (40%)</td> </tr> <tr> <td>Ever</td> <td>86 (40%)</td> <td>107 (43%)</td> </tr> <tr> <td>Current</td> <td>55 (26%)</td> <td>43(17%)</td> </tr> </tbody> </table> <p>p=0.08</p>		Patients N=219	Controls N=254	Never	74 (34%)	100 (40%)	Ever	86 (40%)	107 (43%)	Current	55 (26%)	43(17%)	IV	<p>Some referral bias of patients likely (per authors) Self-selection bias of controls is likely: may select for healthier or more health-conscious controls. Smoking effect is an incidental finding, not part of a planned analysis, that could be due to biases or chance alone.</p>
	Patients N=219	Controls N=254															
Never	74 (34%)	100 (40%)															
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3.	[7]	<p>Exploratory case-control study <u>Cases:</u> 95 referral clinic patients with ALS, enrolled between April 1998 and August 2002. <u>Controls:</u> 106 non-blood relatives (51), or friends or unrelated. An effort made to age-match the controls <u>Exposure:</u> Patients and controls completed an extensive risk factor questionnaire, assessing 34 putative susceptibility factors. Number of questions not stated. Specific questions about smoking not provided directly; some may be inferred from results</p>	<p>The age of quitting smoking was slightly higher in cases than in controls. OR 1.04 95% CI 1.00-1.09; p=0.049</p> <p>The following smoking-related factors were not significant: Cigarette packs per day: 0.97 (0.91-1.03) Smoking: 1.19 (0.67-2.11) Smoking start age: 1.03 (0.91-1.15)</p> <p>Raw data not shown.</p>	V	<p>The patient sample is non-representative. The control sample is non-representative. Overmatching. There appear to be more questions than patients. The methods of this study do not permit any inferences to be drawn from it with regards to risk factors for ALS.</p>												
4.	[8]	<p>Retrospective subgroup analysis in a subset of the Swedish Construction Workers Cohort, established 1971. <u>Population:</u> Initially 300,637 workers registered from 1978-1993. After exclusions (14,982 women and 5097 erroneous registrations): 280,558 men remained. Mean age at entry 35.5 years (66% under age 40 years) <u>Exposure:</u> Detailed information about smoking and snuff-dipping obtained at enrollment via personal</p>	<p><u>Case-finding:</u> 160 incident cases of ALS / 5,505,849 person-years of observation (Crude IR 2.91/100,000 person-years). <u>Age standardized IR</u> 3.50 in non-tobacco users, 2.70 in tobacco smokers and 1.64 in pure snuff dippers.. <u>Compared to non-smokers, age adjusted RR</u> for tobacco smoking 0.8 (95% CI 0.6-1.1) and for pure snuff-dipping 0.6 (95% CI 0.3-1.5).</p>	IV	<p>Results appear to be influenced excessively by large proportion of individuals aged under 40 at enrollment. Mean age at entry 35.5+ mean duration of follow-up 19.6 = mean age at end of observation period 55.5. I think that the data from young</p>												

		<p>interview by nurses. Non-users: 31.4%; Pure snuff dippers: 13.6%; pure smokers: 37.7%; mixed smokers and snuff dippers: 17.3% Snuff-dipping more common among young workers, smoking more common among older workers. <u>Dose calculations:</u> 1 cigarette = 1 gram of tobacco; 1 cigar = 5 grams of tobacco. Expressed as grams per day. <u>Case Finding:</u> Cases of ALS found through record linkage to the Swedish Inpatient Register, using the national registration number, omitting the first two years of complete coverage by the register in each county, to exclude prevalent cases. Additional record linkage to the Causes of Death Register and to the Migration Register. <u>Follow-up:</u> From registration till date of first ALS diagnosis, death, emigration, immigration to a county without or with incomplete Inpatient Registry, or end of follow-up (December 31, 2004). Mean duration of follow-up 19.6 years. <u>Primary outcome variable:</u> Estimated RR and 95% CI using Cox proportional hazards regression models, based on ALS age-standardized incidence rates within different exposure strata.</p>	<p><u>Points to consider:</u> Only 14,821 individuals age 60+ at entry, and 33,073 aged 50-59. Age specific IR 5 or greater for patients >50. Mean time between first diagnosis and death: 323 days. Median: 147 days.</p>		<p>individuals cannot be relied on to infer life-time risk of tobacco use, as they have not entered the age when most of the risk of ALS manifests itself. Characteristics of diagnosis to death data suggest that the cases came mainly from the older individuals. Tobacco use patterns differed between older and younger individuals (an age by exposure interaction). I think the analysis should have been stratified, and performed separately for patients aged over and under 55 years of age at enrollment. Accuracy of responses to nurses' questions not confirmed independently, and changes over time not accounted for.</p>
5.	[11]	<p>Exploratory case-control study. <u>Cases:</u> 186 ALS patients, 87% of 214 eligible patients out of 274 patients ((75%). Definite or Probable ALS, excluding "familial PMA." From 2000 to 2005, from 6 referral centers in the Tokai area. <u>Controls:</u> 366 gender- and age- and district matched, randomly-selected community controls. From 732 eligible controls contacted, 550 (75%) were enrolled; of these 430 completed the questionnaire (78%); of these 366 (85%) were used as controls <u>Exposure assessment:</u> A structured, self-administered questionnaire specifically designed for this study was distributed and collected by mail. It assessed many life-</p>	<p>Analysis is based on 153 cases (82% of 186) and on 306 controls (84% of 366). Proxy respondents in approximately half of cases 48.1% of cases and 48.5% of controls were current smokers (OR=1.0, 95%CI = 0.6-1.3)</p>	IV	<p><u>Limitations, biasing OR to 1.0:</u></p> <ol style="list-style-type: none"> 1. Overmatching, by matching on district 2. High rate of non-enrolees and non-respondents: a risk that patients with unhealthy lifestyles may choose not to respond. 3. No verification of accuracy of tool and of accuracy of responses 4. One answer for an entire 3 year period cannot

		<p>style factors, for patients within the 3 years before onset of ALS and, for controls – within the 3 years before filling the questionnaire.</p> <p>Smoking status was classified as current smokers and non-smokers (including former smokers).</p> <p><u>Analysis:</u> ORs and 95% CIs were calculated by multiple conditional logistic regression</p>			<p>capture changes within that period, and introduces ambiguity.</p> <ol style="list-style-type: none"> 5. ALS may cause patients to quit smoking, as early fatigueability is one of its early symptoms. 6. In discussion authors state “We have confirmed that none of the respondents exhibited any significant change in their lifestyle between a period of 3 and 10 years prior to disease onset” but do not say how they did it. 7. Lumping “never smokers” and “former smokers” is a mistake. Did not permit comparison of current smokers to “never smokers”
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Table e-1. Evidence Table for Class IV and Class V evidence articles published 2003-2009 regarding the association of smoking and ALS.

Legend: CPS II = Cancer Prevention Study II. RR= relative risk. WFN = World Federation of Neurology. (WFN criteria = El Escorial criteria). OR = odds ratio. IR = incidence rate. CI = confidence interval.