Lifetime occupation, education, smoking, and risk of ALS

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ABSTRACT

Objective: To investigate the association between cigarette smoking, level of education, occupation, and the occurrence of sporadic amyotrophic lateral sclerosis (ALS).

Methods: A total of 364 patients and 392 controls completed a questionnaire covering smoking habits, level of education, and occupational history. Main occupations were coded according to the International Standard Classification of Occupations and compared between patients and controls.

Results: The univariate analysis showed an increased risk of developing ALS among current cigarette smokers (OR = 1.7; 95% CI = 1.1 to 2.6; $p = 0.01$), those with a low level of education (elementary school) (OR = 2.2; 95% CI = 1.2 to 3.8; $p < 0.01$), and among women whose main occupation was classified as crafts and related trades workers (OR = 8.4; 95% CI = 1.0 to 70.1; $p = 0.05$). Multivariate analysis (with covariates age, smoking, education, and occupation) showed an increased risk for current smokers of cigarettes (OR = 1.6; 95% CI = 1.0 to 2.5; $p = 0.04$).

Conclusions: Occupation, education, and cigarette smoking are risk factors for amyotrophic lateral sclerosis, but only smoking appeared independently associated. ***Neurology*® 2007;69:1508–1514**

GLOSSARY

ALS = amyotrophic lateral sclerosis; **ILO** = International Labor Organization; **ISCO** = International Standard Classification of Occupations; **JEM** = job-exposure matrix.

Sporadic amyotrophic lateral sclerosis (ALS) is considered to be a multifactorial disease with multiple genetic and environmental factors causing motor neuron degeneration.[1,2] Recently demonstrated associations between ALS and paraoxonase gene polymorphisms, which play a role in biochemical pathways of detoxification and protection against oxidative stress, illustrate that genetic susceptibility combined with exposure to environmental agents may precipitate sporadic ALS.[3,4]

Occupation can be seen as a surrogate for a variety of environmental exposures and can be studied more easily than actual exposure to specific toxic substances, radiation, or other exogenous exposures.[5] Evaluation of the occurrence of sporadic ALS within occupational groups may provide leads to detecting risk factors for ALS. Many studies examined the association between occupations and ALS, but most had methodologic limitations.[6-13] Often, register data were used, conclusions were drawn based on small numbers of exposed individuals, or analyses were not adjusted for level of education, which is an indicator of socioeconomic status and a proxy for other confounders of environmental exposures.[6-13] Moreover, only one group adjusted for cigarette smoking,[8,9] the only exogenous risk factor that has been consistently associated with sporadic ALS in recent population-based studies.[14] The aim of this study was to study the independent

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effect of cigarette smoking, education, and lifetime occupation on the risk of developing ALS.

METHODS **Patients and controls.** Between January 1, 2001, and December 31, 2005, all newly diagnosed patients with sporadic ALS at the University Medical Center Utrecht, a tertiary referral clinic in The Netherlands, were eligible for recruitment. Diagnosis was made according to the El Escorial Criteria after exclusion of other conditions.[15] Age at and site of onset of disease were recorded. Onset of disease was defined as the time of initial weakness, dysarthria, or dysphagia.

To enhance participation and maximize our response rate, acquaintances were selected as our control group. Each case was asked to approach one or two individuals meeting the following criteria: 1) not a spouse, partner, or blood relative, 2) age difference of 5 years or less, 3) same sex.

Data collection. Using a questionnaire, data on age, sex, level of education, cigarette smoking, and lifetime history of occupations were recorded. This questionnaire was a modified version of that used in the association study between physical activity and ALS.[16] Individuals were categorized as 1) current smokers, 2) former smokers, and 3) never smokers. Lifetime consumption of cigarettes was expressed in pack-years. Three levels of education were established: 1) elementary school, 2) middle/high school, and 3) college/university. Individuals were asked to list all occupations held during life and the duration of each occupation as well as the tasks performed. Among patients, only data before onset of symptoms were analyzed. Questionnaires were coded and data were gathered in a blinded fashion. The study protocol was approved by the institutional ethical committee of the University Medical Center Utrecht.

Classification of occupations. All occupations were coded according to the most recently updated version of the International Standard Classification of Occupations (ISCO-88) adopted by the International Labor Organization (ILO), a United Nations specialized agency. The ISCO-88 is a hierarchical coding system, which classifies jobs into occupational groups according to similarity in skill level and specialization of tasks and duties performed (www.ilo.org). Ten major groups at the top level of aggregation, subdivided into 28 sub-major groups, 116 minor groups, and 390 unit groups, can be distinguished. The occupation held for the longest period of time was extracted for each case and control and considered to be the main occupation.

Statistical analysis. The association between risk of ALS and cigarette smoking, level of education, and main occupation was first evaluated by univariate logistic regression. Consequently, multivariate logistic regression was performed using covariates cigarette smoking, level of education, and ISCO major group (of main occupation). All categorical variables were analyzed using dummy variables. Reference groups were chosen by the following criteria: 1) a similar distribution in patients and controls (a similar frequency of a specific variable among patients and controls, OR $\approx$ 1); 2) represented by sufficient numbers of individuals; and 3) in case of a hierarchical system, either the lowest or highest category.

To assess potential dose-response effects of smoking, the number of pack-years was recoded into tertiles based on control data (>22.5 pack-years, 10 to 22.5 pack-years, and <10 pack-years) and evaluated by univariate logistic regression in former and current smokers.

Because the ISCO-88 is a classification system according to skill and specialization, men and women represent different occupations in each ISCO major group. For example, in the group craft and related trades workers (major group 7), men predominantly represent metal and machinery workers whereas women represent textile workers. Moreover, men and women within the same occupation may have different levels of environmental exposure due to differences in tasks. Men and women were therefore analyzed separately. To check whether individual occupations stood out, we also compared frequencies of sub-major, minor, and unit groups of main occupations by logistic regression.

Statistical analysis was conducted by N.A. Sutedja (Department of Neurology) and K. Fischer (Julius Center for Health Sciences and Primary Care), University Medical Center Utrecht.

RESULTS **Subjects.** A total of 364 of 482 ALS (76%) and 392 of 498 control (79%) questionnaires were returned. Patient characteristics of participants and nonparticipants were similar. Characteristics of the patients and controls are shown in table 1. Mean age and sex were similar in patients and controls. In patients with ALS, site of onset and the El Escorial Criteria at diagnosis were similar to those reported in previous population-based studies.[17,18]

Cigarette smoking. Compared to nonsmokers, current smokers had an increased risk of ALS both in the univariate analysis (OR = 1.7; 95% CI = 1.1 to 2.6; $p = 0.01$) and independent of age, level of education, and occupation (OR = 1.6; 95% CI = 1.0 to 2.5; $p = 0.04$) (table 2). In smokers, no exposure-response relation for cigarette smoking was observed (highest tertile [>22.5 pack-years] vs lowest tertile [<10 pack-years]) (OR = 0.8; 95% CI = 0.6 to 1.5; $p = 0.9$).

When analyzing men and women separately, current smokers had an increased risk of ALS in women in the univariate analysis (OR = 2.0; 95% CI 1.0 to 3.8; $p = 0.04$). The risk of ALS for current smokers was also increased but no longer significant in women after adjusting for age, level of education, and occupations (OR = 1.7; 95% CI 0.9 to 3.6; $p = 0.1$) as well as in men both in the univariate analysis (OR = 1.5; 95% CI = 0.9 to 2.6; $p = 0.2$) and independent of age, level of education, and occupation (OR = 1.5; 95% CI = 0.8 to 2.7; $p = 0.2$).

Education. Compared to individuals with the highest level of education, individuals with the lowest level of education (elementary school) had

Table 1 Characteristics of patients with amyotrophic lateral sclerosis (ALS) and controls

	ALS, n = 364	Controls, n = 392	*p*
Age, y, mean ± SD (range)	60.2 ± 11.7 (24–83)	60.0 ± 10.9 (27–83)	0.8
Male, n (%)	229 (63)	228 (58)	0.2
Age at onset, y, mean	58.0		
Site of onset, n (%)			
Bulbar	96 (28)		
Spinal			
Cervical	116 (33)		
Thoracal	3 (10)		
Lumbosacral	127 (37)		
Multiple regions	6 (2)		
El Escorial criteria,* n (%)			
Definite ALS	80 (23)		
Probable ALS	161 (47)		
Possible ALS	70 (20)		
Suspected ALS	34 (10)		

*At diagnosis.
Age at onset was missing in 1 patient; site at onset was missing in 16 patients; El Escorial criteria were missing in 19 patients. Age was missing in 3 controls.

a significantly increased risk of ALS in the univariate analysis (OR = 2.2; 95% CI = 1.2 to 3.8; $p < 0.01$) (table 2). This OR was slightly lower and no longer reached statistical significance when adjusted for confounders (adjusted OR = 1.8; 95% CI = 0.9 to 3.6; $p = 0.1$).

Occupation. In men, the distribution of the ISCO major groups of the main occupation was similar in patients and controls. Women whose main occupation was categorized into ISCO major group 7 (craft and related trades workers) had a significantly increased risk of ALS in the univariate analysis (OR = 8.4; 95% CI = 1.0 to 70.1; $p = 0.05$) (table 2).

Because only taking into account the main occupation held during their lifetime might have resulted in the potential omission of effects of short-term occupational exposures, we repeated the univariate logistic regression analysis for the ISCO major group of all occupations held. In men, 229 patients held 582 occupations and 228 controls held 509 occupations: no association with ALS for any of the ISCO major groups was found. In women, 135 patients held 259 occupations and 164 controls held 317 occupations: an association of major group 7 and ALS (OR = 3.0; 95% CI 1.1 to 8.0; $p = 0.03$) was found.

Multivariate analyses were performed for main occupation only. After adjustment for age, smoking, and level of education, the risk of ALS for women whose main occupation was categorized into ISCO major group 7 was still considerably increased (OR = 6.2), but no longer significant (95% CI = 0.7 to 55.0; $p = 0.1$) (table 2). Seven of the nine women whose main occupation was classified into major group 7 (craft and related trades workers) were categorized as submajor group 74 ("other craft and related trades workers"), 6 in minor group 743 ("textile, garment, and related trades workers"), and 1 in 741 ("food processing and related trades workers"). However, none of the subcategories of ISCO major group 7 or any other ISCO major group showed a significant association with ALS. Among the women, the ISCO major group 7 subgroups with the highest OR were submajor group 74 "other crafts and related trades workers" (OR = 8.7; 95% CI = 0.9 to 81.7; $p = 0.06$) and minor group 743 "textile, garment and related trades workers" (OR = 7.3; 95% CI = 0.8 to 70.0; $p = 0.09$).

DISCUSSION This study of 364 patients and 392 controls shows that currently smoking cigarettes is an independent risk factor for sporadic ALS. Individuals with a low level of education—a proxy for low socioeconomic status—and women working in craft and related trades showed an increased risk of developing ALS. Smoking may have accounted for a certain degree of these associations because in the multivariate analysis, smoking was the only factor that was indepen-

Table 2 Distribution of smoking, education, and occupational groups in patients and controls: Crude and adjusted OR

	ALS, n (%)	Controls, n (%)	Crude OR (95% CI)*	p	Adj. OR (95% CI)*	p
Total group	n = 364	n = 392				
Smoking						
Current	78 (22)	54 (14)	1.7 (1.1–2.6)	0.01†	1.6 (1.0–2.5)	0.04†
Former	146 (42)	174 (46)	1.0 (0.7–1.4)	0.95	1.0 (0.7–1.4)	0.9
Never	128 (36)	151 (40)	1.0	1.0		
Educational level						
Elementary school	46 (13)	27 (7)	2.2 (1.2–3.8)	<0.01†	1.8 (0.9–3.6)	0.1
High school	237 (66)	264 (68)	1.1 (0.8–1.6)	0.5	1.0 (0.7–1.6)	0.9
College/university	75 (21)	95 (25)	1.0	1.0		
Men only	n = 229	n = 228				
ISCO major group						
0 Armed forces	4 (2)	5 (2)	0.9 (0.2–3.5)	0.8	0.8 (0.2–3.4)	0.8
1 Legislators, senior officials and managers	44 (20)	48 (22)	1.0	1.0		
2 Professionals	35 (16)	41 (18)	0.9 (0.5–1.7)	0.8	1.0 (0.5–1.9)	0.96
3 Technicians and associate professionals	23 (10)	38 (17)	0.7 (0.3–1.3)	0.2	0.6 (0.3–1.2)	0.1
4 Clerks	24 (11)	19 (9)	1.4 (0.7–2.9)	0.4	1.1 (0.5–2.4)	0.8
5 Service workers and shop and market sales workers	9 (4)	14 (6)	0.7 (0.3–1.8)	0.5	0.7 (0.2–1.7)	0.4
6 Skilled agricultural and fishery workers	10 (5)	9 (4)	1.2 (0.5–3.3)	0.7	0.9 (0.3–2.5)	0.8
7 Craft and related trades workers	46 (21)	33 (15)	1.5 (0.8–2.8)	0.2	1.1 (0.1–2.1)	0.8
8 Plant and machine operators and assemblers	20 (9)	12 (5)	1.8 (0.8–4.1)	0.2	1.5 (0.6–3.7)	0.4
9 Elementary occupations	6 (3)	4 (2)	1.6 (0.4–6.2)	0.5	1.0 (0.2–4.2)	0.98
Women only	n = 135	n = 164				
ISCO major group						
0 Armed forces	0 (0)	0 (0)				
1 Legislators, senior officials and managers	7 (6)	6 (4)	1.2 (0.4–3.9)	0.7	1.3 (0.4–4.3)	0.7
2 Professionals	21 (17)	35 (22)	0.6 (0.3–1.3)	0.2	0.7 (0.3–1.5)	0.3
3 Technicians and associate professionals	7 (6)	19 (12)	0.4 (0.1–1.0)	0.1	0.4 (0.1–1.1)	0.1
4 Clerks	24 (20)	42 (27)	0.6 (0.3–1.2)	0.1	0.6 (0.3–1.2)	0.1
5 Service workers and shop and market sales workers	41 (34)	43 (28)	1.0	1.0		
6 Skilled agricultural and fishery workers	2 (2)	3 (2)	0.7 (0.1–4.4)	0.7	1.1 (0.1–8.9)	0.9
7 Craft and related trades workers	8 (7)	1 (1)	8.4 (1.0–70.1)	0.05†	6.2 (0.7–55.0)	0.1
8 Plant and machine operators and assemblers	1 (1)	1 (1)	1.0 (0.1–17.3)	0.97	1.3 (0.1–21.3)	0.9
9 Elementary occupations	11 (9)	6 (4)	1.9 (0.7–5.7)	0.2	1.6 (0.5–4.9)	0.4

Information on smoking habits was missing in 12 patients and 13 controls; level of education was missing in 6 patients and 6 controls; data on longest occupation were missing in 21 patients and 13 controls. In men: information on smoking habits was missing in 8 patients and 8 controls; level of education was missing in 4 patients and 5 controls; data on longest occupation were missing in 8 patients and 5 controls. In women: information on smoking habits was missing in 4 patients and 5 controls; level of education was missing in 2 patients and 1 control; data on longest occupation were missing in 13 patients and 8 controls.

*Computed by logistic regression adjusting for age, smoking, level of education, and ISCO major group.

†$p < 0.05$.

dently related to ALS. However, these findings must be interpreted with caution due to the comparable ORs in the univariate and multivariate analyses.

Our finding that current smoking is associated with sporadic ALS is in agreement with an evidence-based evaluation of the role of exogenous risk factors in sporadic ALS which suggested

cigarette smoking to be a probable ("more likely than not") risk factor based on findings in two population-based studies.[14] In agreement with our study, some studies found a significantly increased risk of ALS for current smokers, but not for former smokers.[19,20] However, our findings appear in contrast to those reported in another case-control study, suggesting increased risk of ALS for former smokers but not for current smokers.[21] These discrepancies can probably be attributed to the absence of a standard definition of former smokers.

Cigarette smoke might influence the risk of ALS in a genetically susceptible individual by either a direct neurotoxic effect on motor neurons or by increasing oxidative stress. Cigarette smoke contains numerous toxic chemicals and might influence the risk of ALS in a genetically susceptible individual by either a direct neurotoxic effect on motor neurons or by increasing oxidative stress.[20] Previously, a strong interaction between smoking and the PON2 C311S polymorphism has been shown in myocardial infarction risk; because this polymorphism also appears to be associated with sALS, it is conceivable that such an interaction may also play a role in sALS.[3,4]

In this study, both male and female current smokers showed an increased risk of ALS. Previous studies have produced conflicting results on differences in ALS risk among smokers between men and women. The underlying mechanism of motor neuron disease caused by exposure to cigarette smoke is more likely to be the same in both men and women. As discussed in a previous study,[20] there is no explanation for differences between men and women in ALS risk for smokers.

The presence of a dose-effect association would strengthen the argument in favor of a direct link between ALS and tobacco consumption. Dose-response effects of smoking and ALS have been demonstrated in one previous study,[19] but not in others,[20,21] including the present study. A possible explanation for the lack of a dose-effect association in this study could be misclassification. Although smoking habits during lifetime were recorded as accurately as possible, this study was performed retrospectively and prone to recall difficulties. Misclassification could have resulted in dilution of the effect. Alternatively, a dose-response effect could be truly absent, as shown previously,[20] and smoking status could be a marker for an unknown risk factor.

Level of education or socioeconomic status have only infrequently been studied as risk factors for ALS. Two case-control studies showed inconsistent findings.[22,23] A large population-based study showed a lack of association between social class of patients with ALS and controls.[22] An older case-control study performed between 1964 and 1982 showed a low level of education to be associated with an increased risk of ALS.[23] Other epidemiologic studies have suggested both an increased risk of ALS with higher levels of education[24] and a lack of association of level of education with ALS.[25] However, these studies did not adjust for smoking and so a higher prevalence of smoking among lower socioeconomic groups may provide the explanation for these inconsistent findings.[26]

Occupations have been studied more extensively in patients with ALS. Over 50 studies have been performed and a variety of occupations have been thought to be associated with ALS.[6-13] Two occupations that have been put forward most recently are soccer players and military workers.[27,28] The results on soccer players were based on a comparison between only five and eight exposed patients with ALS with ALS mortality rate in the general population,[6,7] generating a relatively low level of evidence.[14] A large prospective study suggested that military workers were at increased risk[8]; however, the diagnosis of ALS was based on register information and this difference in study design makes a comparison with our study difficult. Moreover, the increased risk of ALS in Gulf War veterans was based on a few (18) exposed individuals.[10]

In the present study, we attempted to identify individual as well as groups of occupations with increased ALS risk. We were not, however, able to confirm any previously suggested occupations as risk factors. Crafts and related trades work (predominantly in the textile and garment industry) might be a risk factor for developing ALS in women, but this study was not able to show a significant association in the multivariate analysis. Because occupational categories are heterogeneous and consist of relatively small numbers of individuals, a larger study with more power may be needed to demonstrate professions associated with sporadic ALS with higher degree of certainty.

No previous study on occupation has presented the effect of occupational risk adjusting for the important confounders education—as a proxy of socioeconomic status—and smoking. In the present study, occupation was not an independent risk factor, emphasizing that it is important to adjust for education and cigarette smoking. Moreover, assessment of occupations was more

accurate than in other studies as lifetime occupational history was used in combination with a standardized occupation system. An analysis which took the full occupational history into account did not result in different findings. Also, ALS was established by clinical data rather than register data. Only data prior to onset of disease were analyzed in this study.

Our control population was matched according to age and sex. A control group of acquaintances could result in underestimation of association. Overmatching might have occurred and bias could be in either direction. However, we were able to replicate the finding in studies which did not use a self-selected control group that smoking was independently associated with the risk of developing ALS.[19-21] This study has demonstrated the importance of studying the effect on occurrence of ALS of smoking, education, and occupation in a single model. Larger prospective studies are needed to further elucidate these relationships. To provide greater insight into exogenous risk factors, larger (preferably population-based) studies may be needed, using a job-exposure matrix (JEM). A JEM enables the linking of occupations to profiles of environmental exposures by providing (semi-)quantitative assessments of various exogenous exposures (for example heavy metals, solvents, electromagnetic fields) for each occupation. JEM studies that have been performed in patients with ALS have involved electromagnetic radiation. These have, however, been small[29] or have determined the outcome ALS by use of registers[30] and results may be inconsistent. The applications of more JEM studies to ALS will enable us to compare exposure to various environmental agents between patients and controls and hopefully elucidate which of these environmental exposures increases the risk of ALS.

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