Original Contribution

Smoking, Alcohol Consumption, and the Risk of Amyotrophic Lateral Sclerosis: A Population-based Study

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Initially submitted July 25, 2011; accepted for publication January 11, 2012.

Smoking has been posited as a possible risk factor for amyotrophic lateral sclerosis (ALS), but large population-based studies of patients with incident disease are still needed. The authors performed a population-based case-control study in the Netherlands between 2006 and 2009, including 494 patients with incident ALS and 1,599 controls. To prove the relevance of population-based incidence cohorts in case-control studies, the authors compared results with those from cohorts including patients with prevalent ALS and referral patients. Subjects were sent a questionnaire. Multivariate analyses showed an increased risk of ALS among current smokers (odds ratio = 1.38, 95% confidence interval (CI): 1.02, 1.88) in the incident patient group only. Cox regression models showed that current smoking was also independently associated with shorter survival (hazard ratio = 1.51, 95% CI: 1.07, 2.15), explaining the lack of association in the prevalent and referral patient groups. Current alcohol consumption was associated with a reduced risk of ALS (incident patient group: odds ratio = 0.52, 95% CI: 0.40, 0.75). These findings indicate that current smoking is associated with an increased risk of ALS, as well as a worse prognosis, and alcohol consumption is associated with a reduced risk of ALS, further corroborating the role of lifestyle factors in the pathogenesis of ALS. The importance of population-based incident patient cohorts in identifying risk factors is highlighted by this study.

alcohol drinking; amyotrophic lateral sclerosis; smoking

Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; OR, odds ratio.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of motor neurons leading to progressive weakness of the limbs, bulbar muscles, and respiratory muscles. Fifty percent of patients die within 3 years after onset of symptoms, mainly due to respiratory failure (1, 2). Motor neuron degeneration in sporadic ALS is considered to be a multifactorial process consisting of both genetic and environmental factors (3, 4). The elucidation of pathogenic factors may provide new targets for developing treatment strategies.

Several studies have investigated environmental risk factors, but only smoking has consistently been posited as a possible risk factor. Cigarette smoke could increase the risk of developing ALS through several mechanisms, including inflammation, oxidative stress, and neurotoxicity caused by heavy metals and other chemical compounds present in cigarette smoke (5). In addition, other confounding lifestyle factors could be involved—for example, alcohol consumption. Previous studies and 2 recent reviews have investigated the relation between smoking as a risk factor and ALS based on the best available research, with the authors concluding that smoking could be a risk factor for ALS (6–9). All previously executed studies, however, had methodological drawbacks negatively affecting the level of evidence, including small or selected study samples, the use of death certificate data, and insufficient account of potentially confounding factors such as educational level and alcohol consumption. Therefore, according to published evidence-
based criteria, class I evidence of an association between smoking and ALS has not yet been provided (6).

Because ALS is a rare disease with a mean incidence of 1–2 cases per 100,000 population per year, large, well-designed population-based case-control studies of ALS are difficult and time-consuming to perform (10). The aim of our study was to provide class I evidence for a possible relation between smoking and/or alcohol consumption and ALS in a large, representative, prospectively recruited incident patient group in comparison with age-, sex-, and geographically matched population-based controls.

MATERIALS AND METHODS

Patients and controls

From January 1, 2006, to June 30, 2009, we performed a population-based study (Prospective ALS Study the Netherlands) aiming at complete ascertainment of all patients with ALS in the Netherlands. Patients with ALS were recruited through multiple sources (neurologists, rehabilitation physicians, patient support associations, and a website (http://www.als-centrum.nl/)). The Netherlands, with 16.3 million inhabitants as of January 1, 2006 (Netherlands Central Bureau of Statistics, unpublished data (http://www.cbs.nl/nl-NL/menu/home/default.htm)) and an area of 41,528 km², is a densely populated country. The accessibility of health care to all inhabitants and a well-developed infrastructure provide ideal circumstances for a population-based study. Patients who were diagnosed as having possible, probable (laboratory-supported), or definite ALS according to the revised El Escorial Criteria were included in our study after exclusion of other conditions (11). ALS patients with family members who had been affected by ALS were excluded.

To explore the relevance of using population-based incident patient cohorts for studying susceptibility or disease-modifying factors in ALS, we included several patient groups in the analyses. Patients recruited for the population-based study and diagnosed with ALS on or after January 1, 2006 (“onset population-based study”) were considered the “incident patient group.” Patients who were recruited for the population-based study and diagnosed before January 1, 2006, but were alive after that date constituted the “prevalent patient group.” To obtain the largest possible patient group (“total patient group”), we combined the incident and prevalent patient groups with a previously studied group of patients who were diagnosed with sporadic ALS between January 1, 2001, and December 31, 2005, at the University Medical Center Utrecht, a tertiary-care referral clinic in the Netherlands (12). There was a partial overlap between the latter patient group and the prevalent patient group.

Population-based ascertainment of controls is important in order to ensure a representative sample of the general population and to prevent overmatching. Controls were recruited through the general practitioners of the participating patients. The Dutch health-care system ensures that all inhabitants of the Netherlands are registered with a general practitioner. The general practitioner was asked to send information about our study to persons listed below the patient in the alphabetized register, matched for gender and age (±5 years). To prevent overmatching, spouses or blood relatives of the patient were not eligible to be controls.

After giving informed consent, the patients and controls were included in our study and were sent the questionnaire. Ethics approval was provided by the institutional review board of the University Medical Center Utrecht.

Data collection

Data on cigarette smoking, highest level of education, and alcohol consumption were recorded by questionnaire. This questionnaire was a modified version of that used in a previous study on the relation of smoking to education and occupation (12). Detailed data were collected on age at the start and cessation of smoking and alcohol consumption, as well as the daily numbers of cigarettes smoked and units of alcohol consumed. Smoking and alcohol consumption status were categorized as never, former, or current at the time of disease onset (i.e., before diagnosis). Current smoking or current alcohol consumption was defined as smoking or drinking at the time of onset of muscle weakness or swallowing/speech difficulties. Lifetime cigarette smoking was expressed in pack-years (number of packs of cigarettes × years spent smoking, defining a pack as 20 cigarettes). Lifetime consumption of alcohol was expressed as the total number of units of alcohol consumed. Information about the amount of red wine consumed was also recorded, because of its potential antioxidant effect. Three levels of education were established: 1) elementary school, 2) middle/high school, and 3) college/university.

All questionnaires were coded prior to processing and analysis, ensuring blinding. Response rates were recorded for both patients and controls. Additionally, the persons gathering the data were blinded with regard to the hypotheses being tested. If data were found to be missing or inconsistent in the submitted questionnaires, patients and controls were contacted by telephone to complete the information or correct inconsistencies. Data entry was automated by importing corrected questionnaires into the database using a scanner.

Statistical analysis

The associations between smoking and alcohol consumption and risk of ALS were first evaluated by means of univariate analysis using logistic regression. Subsequently, multivariate logistic regression was performed to establish the relations among smoking, alcohol consumption, and ALS risk, using age, gender, and educational level as covariates. Odds ratios and 95% confidence intervals were derived from these analyses. Pack-years of smoking were analyzed as a continuous variable but were also analyzed after being recoded into quartiles based on control data. In addition, we performed analyses to investigate a possible nonlinear relation. We investigated the interaction between gender and smoking status by introducing an interaction term in the multivariate analyses.

To estimate the latency between disease onset and symptom onset in ALS patients, we performed the following regression analysis: Smoking status was calculated for
each individual per 5-year interval, for the 40 years preceding symptom onset for patients and preceding the date of inclusion for controls. For each 5-year interval before this reference date, the adjusted odds ratio was calculated for current smoking versus never smoking. Patients and controls were considered to be at risk of smoking at a minimum age of 12 years.

Cox regression models were fitted to investigate the roles of smoking and alcohol consumption in the risk of dying of ALS. Hazard ratios and 95% confidence intervals were derived from these analyses. Smoking status, duration of smoking, time since quitting smoking, and number of pack-years were used as variables. Alcohol use, duration of alcohol use, and the number of glasses of alcohol consumed daily were also used as variables. Known prognostic factors, including gender, age, and site of onset, were included as covariates. Forced vital capacity at the time of diagnosis is also a well-known prognostic factor and was included as a covariate for the patients in whom vital capacity was measured using a standardized technique (13, 14).

RESULTS

Patients

In the population-based study, 749 (81%) of 931 patients and 1,599 (93%) of 1,724 controls returned the questionnaire. Characteristics of 494 incident and 255 prevalent patients from the population-based study and 937 patients in the total group, as well as controls, are shown in Table 1. There was an overlap of 178 patients between the prevalent patient group and 937 patients in the total group, as well as controls, are shown in Table 1. There was an overlap of 178 patients between the prevalent patient group and 937 patients in the total group. Patient characteristics were similar in responders and nonresponders. For incident patients, gender, age, and site of onset were similar in controls and patients from previous European population-based studies (10). Compared with the incident patient group, prevalent patients had significantly lower ages at disease onset ($P<0.001$) and inclusion ($P=0.01$), disease duration was significantly longer ($P<0.001$), and spinal site of onset was significantly more frequent ($P=0.007$). The patients diagnosed in our tertiary-care referral center had a significantly lower age at onset (59 years, $P<0.001$) than the population-based recruited patients.

Smoking

Multivariate analyses in incident patients showed an increased risk of ALS among current smokers (odds ratio (OR) = 1.38, 95% confidence interval (CI): 1.02, 1.88) (Table 2). The odds ratios were similar in separate analyses for men (OR = 1.48, 95% CI: 0.98, 2.25) and women (OR = 1.47, 95% CI: 0.90, 2.38). No dose-response relation could be established: Median numbers of pack-years were similar in patients (15.0 pack-years; range, 0.1–108) and controls (15.0 pack-years; range, 0.1–122.5), as were pack-years categorized into quartiles and pack-years entered into nonlinear analyses. In addition, the median number of years since quitting smoking (23 years (range, 1–58) vs. 24 years (range, 1–60)) and the median total duration of smoking (22 years (range, 1–60) vs. 26 years (range, 1–68)) did not differ significantly between patients and controls. No significant association of current smoking with risk of ALS was found in the prevalent patient group or the total patient group (Table 2).

The median duration of follow-up for survival analysis in the total patient group was 2.9 years (range, 0.1–30). We determined smoking status (ever, never, or current) and calculated the concomitant odds ratio for current smoking as

Table 1. Characteristics of ALS Patients and Controls, Prospective ALS Study the Netherlands, 2006–2009

<table>
<thead>
<tr>
<th>ALS Patient Group</th>
<th>Incident Patients a (n = 494)</th>
<th>Prevalent Patients b (n = 255)</th>
<th>Total c (n = 937)</th>
<th>Controls (n = 1,599)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Median (Range)</td>
<td>% Median (Range)</td>
<td>% Median (Range)</td>
<td>% Median (Range)</td>
</tr>
<tr>
<td>Male gender</td>
<td>62.1 58.0 (25–89)</td>
<td>61.7 58.0 (25–89)</td>
<td>62.7 58.0 (20–91)</td>
<td></td>
</tr>
<tr>
<td>Age at study inclusion, years</td>
<td>63.8 (25–89)</td>
<td>61.4 (27–86)</td>
<td>62.9 (25–89)</td>
<td>62.7 (20–91)</td>
</tr>
<tr>
<td>Age at ALS onset, years</td>
<td>62.4 (23–89)</td>
<td>56.2 (24–82)</td>
<td>61.0 (23–89)</td>
<td>62.7 (20–91)</td>
</tr>
<tr>
<td>Disease duration at diagnosis, years</td>
<td>0.82 (0–11)</td>
<td>1.0 (0–8)</td>
<td>0.89 (0.03–27)</td>
<td>62.7 (20–91)</td>
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<td>Type of ALS onset</td>
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<td>Bulbar</td>
<td>34.8 24.8 (0–11)</td>
<td>31.2 24.8 (0–11)</td>
<td>31.2 24.8 (0–11)</td>
<td>31.2 24.8 (0–11)</td>
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<tr>
<td>Spinal</td>
<td>65.2 75.2 (24–82)</td>
<td>68.8 75.2 (24–82)</td>
<td>68.8 75.2 (24–82)</td>
<td>68.8 75.2 (24–82)</td>
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<tr>
<td>Educational level</td>
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<tr>
<td>Elementary school</td>
<td>9.2 9.8 (0–11)</td>
<td>10.8 9.8 (0–11)</td>
<td>10.8 9.8 (0–11)</td>
<td>10.8 9.8 (0–11)</td>
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<tr>
<td>Middle school/high school</td>
<td>66.6 68.5 (24–82)</td>
<td>66.4 68.5 (24–82)</td>
<td>66.4 68.5 (24–82)</td>
<td>66.4 68.5 (24–82)</td>
</tr>
<tr>
<td>College/university</td>
<td>24.2 21.7 (0–8)</td>
<td>22.8 21.7 (0–8)</td>
<td>22.8 21.7 (0–8)</td>
<td>22.8 21.7 (0–8)</td>
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</table>

Abbreviation: ALS, amyotrophic lateral sclerosis.

a Population-based recruited patients diagnosed with ALS on or after January 1, 2006.

b Population-based recruited patients diagnosed before January 1, 2006, but alive after that date.

c All incident and prevalent patients, combined with a referral population diagnosed between January 1, 2001, and December 31, 2005.
compared with never smoking for every 5-year interval before symptom onset in the 494 incident patients and 1,599 controls (Figure 1). This analysis showed that odds ratios for current smoking as compared with never smoking increased towards the symptom onset date.

Information on vital capacity at diagnosis was available for 567 (61%) of the 931 ALS patients, and decreased vital capacity was significantly associated with shorter survival ($P = 0.026$). In these patients, current smoking was associated with a worse prognosis, with a hazard ratio of 1.51 (95% CI: 1.07, 2.15), adjusted for vital capacity, gender, age, and site of onset (Figure 2). Results were similar for both sexes. Median survival in current smokers was 3.2 years as compared with 4.2 years in never smokers. A sub-analysis was performed in the 185 current smokers. One year after onset of disease, only 10 patients had quit smoking; therefore, a subanalysis of these 185 patients exploring whether cessation of smoking influenced survival lacked statistical power. Nevertheless, patients who continued smoking had a nonsignificantly higher risk of dying (hazard ratio = 1.36, 95% CI: 0.46, 4.02).

Alcohol consumption

Current alcohol consumption was found to be independently associated with a reduced risk of ALS in the incident (OR = 0.52, $P = 6.6 \times 10^{-5}$), prevalent (OR = 0.35, $P = 5.35 \times 10^{-7}$), and total (OR = 0.43, $P = 2.57 \times 10^{-10}$) patient groups. No specific effect of drinking red wine could be identified: The percentage of current drinkers of red wine was not significantly different in patients (58%) versus controls (68%), nor was the median lifetime number of glasses of red wine consumed in patients (6,600; range, 300–77,000) versus controls (9,100; range, 100–152,000), after adjustment for age, gender, smoking, and educational level. There was no significant interaction between alcohol use and smoking. Alcohol consumption was not associated with survival or age at onset of disease.

**DISCUSSION**

This prospective, population-based case-control study in the Netherlands provided evidence that cigarette smoking is independently associated with an increased risk of ALS and that alcohol consumption is independently associated with a reduced risk of ALS. Current smoking is associated with a worse prognosis, after correction for other known prognostic factors, including forced vital capacity. In the present study, we were able to discover a large number of newly diagnosed patients. The use of detailed questionnaires accounting for exposure before disease onset, the use of population-based and matched controls, high response rates, the use of established diagnostic criteria, the quantification of exposures, the elaborate accounting for bias and confounding (including educational level), and the blinding of persons gathering the data on disease status and the hypotheses being tested fulfilled the predefined criteria for class I evidence for these risk factors (6).

Earlier studies showed contrasting results on smoking and ALS; however, class I evidence was still lacking (12, Table 2. Cigarette Smoking and Alcohol Consumption Among ALS Patients and Controls, Prospective ALS Study the Netherlands, 2006–2009

<table>
<thead>
<tr>
<th>Cigarette smoking</th>
<th>% of Controls (n=1,599)</th>
<th>% Adjusted ORd</th>
<th>95% CI</th>
<th>P Value</th>
<th>% of Controls (n=937)</th>
<th>% Adjusted ORd</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
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<tr>
<td>Never smoker</td>
<td>34.6</td>
<td>1 Reference</td>
<td>40.4</td>
<td>0.81</td>
<td>0.58</td>
<td>0.69–1.02</td>
<td>0.075</td>
<td>0.019</td>
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<tr>
<td>Former smoker</td>
<td>45.3</td>
<td>1 Reference</td>
<td>40.3</td>
<td>0.58</td>
<td>0.16</td>
<td>0.08–1.10</td>
<td>0.016</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>19.9</td>
<td>1 Reference</td>
<td>43.3</td>
<td>0.80</td>
<td>0.06</td>
<td>0.02–1.28</td>
<td>0.044</td>
<td>0.009</td>
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<td>13.8</td>
<td>0.83</td>
<td>0.03</td>
<td>0.01–1.98</td>
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<td>16.3</td>
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<td>0.03</td>
<td>0.01–1.98</td>
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Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; OR, odds ratio.

a Population-based recruited patients diagnosed with ALS on or after January 1, 2006.

b Population-based recruited patients diagnosed before January 1, 2006, but alive after that date.

c All incident and prevalent patients, combined with a referral population diagnosed between January 1, 2001, and December 31, 2005.

d Odds ratios were adjusted for age, gender, smoking status, educational level, and alcohol consumption.
A recent meta-analysis showed a moderate association of current smoking with ALS (8). However, most of the studies included in the meta-analysis had recruited prevalent and clinic-based referral patients. In the meta-analysis, current smoking was associated with ALS only in women. Separate analyses for men and women were performed in our study as well, but no gender difference was found. Most likely because of loss of power through a reduction in sample size, the separate odds ratios for men and women were not statistically significant as the odds ratio was in the combined patient group. In another large pooled analysis including patients from 5 different cohorts, smoking was identified as a risk factor for ALS, but a dose-response relation could not be established (9). However, that analysis included only 1 population-based cohort, and data on exposure to cigarette smoke up to disease onset were not available (9).

Our study emphasizes the relevance of performing studies in incident patients to identify susceptibility or disease-modifying factors (environmental or genetic), particularly for diseases such as ALS, which is associated with shortened survival. Patients with less favorable prognostic factors, such as current smoking, are likely to be underrepresented in a prevalent patient group compared with an incident patient group, as shown by the lower frequency of other less favorable prognostic factors (older age, bulbar onset, longer disease duration at diagnosis) in the prevalent cohort of our study (Table 1). This explains why current smoking was independently associated with increased ALS risk only in the incident patient group, not in the prevalent patient group. This effect has previously been described as Neyman’s bias (21). Alcohol consumption was not
associated with a worse prognosis, and consequently no difference was found in the association between alcohol use and risk of ALS in the incident and prevalent groups.

Our results suggest that instead of former smoking habits, premorbid current cigarette smoking is particularly associated with the development of ALS and might act as a “trigger” in a multifactorial cascade. In a previous investigation, the duration of smoking was associated with ALS (16), but this relation could not be confirmed in our study. We performed a regression analysis to explore the time point at which exposure to cigarette smoke was most associated with ALS. This method was also used in previous studies to clarify the relation between physical activity and ALS (22). It showed that current smoking was most strongly associated with an increased risk of ALS towards the onset date of the disease. Since the reference date of our analysis was set at onset of weakness and well before diagnosis, it is highly unlikely that having a diagnosis of ALS influenced current smoking status.

We expected alcohol consumption to be a confounder of smoking, but it appeared to be associated with a reduced risk of ALS independently, and no significant interaction between alcohol consumption and cigarette smoking was found in our study. Previous studies have revealed a potentially neuroprotective effect of constituents of red wine. In vivo experiments carried out in a transgenic mouse model for ALS showed that mice fed lyophilized red wine had significantly increased survival as compared with untreated control animals, possibly because of antioxidant effects or reduced glutamate-induced apoptosis (9, 23). However, the protective qualities of alcohol consumption in our study could not be attributed to consumption of red wine alone, since no difference was found in the amount of red wine consumed by patients as compared with controls. One previous population-based study could not establish a relation between alcohol consumption and ALS, but only 161 patients were included (19). Other, relatively small studies have shown conflicting results but suffered from bias, because only clinic-based referral patients were included or because there was no detailed record on lifetime alcohol consumption (24, 25).

In this study, we accrued a large group of patients and controls. Complete case ascertainment does remain a challenge and could have led to some residual selection bias. However, the characteristics of patients in our study were similar to those of patients in other population-based studies (10). In addition, recall bias might have had an effect on our results, but we minimized this by using structured questionnaires and by telephoning participants to reduce missing data and inconsistencies. Another limitation may be that persons participating in case-control studies are healthier than the general population (the “healthy worker effect”), explaining the lower percentage of current smokers in the control group (7). However, it is not likely that our control group was healthier than the patient group, since alcohol consumption, also considered a bad habit, was overrepresented in controls.

The role of reliable identification of risk factors is 2-fold (7). First of all, if a risk factor has no redeeming features, its identification may lead to its avoidance, with future reduction of disease burden. Although our data are suggestive of a beneficial effect of smoking cessation on survival of ALS patients, this question still needs to be answered in future studies. Second, identification of an established risk factor for ALS can stimulate the generation of hypotheses about the biologic processes that trigger disease initiation, such as increased inflammation, oxidative stress, and neurotoxicity caused by heavy metals or other chemical compounds present in cigarette smoke (5). Exhaled cigarette smoke has also been shown to contain formaldehyde, increased exposure to which has been associated with increased ALS mortality (26). Paraoxonases are esterase enzymes with antioxidative properties that can be inhibited by cigarette smoking. Some polymorphisms associated with loss of paraoxonase function have been found to be associated with ALS onset, and mutations in the paraoxonase gene lead to familial ALS (27). In oncologic studies, progress has been made to identify susceptibility genes which, combined with smoking, have a multiplier effect (28–30). In the future, international collaborative studies on gene-environment interaction among larger numbers of ALS patients may identify genetic variants that increase susceptibility to ALS, where smoking might act as one of several environmental/lifestyle triggers that set off motor neuron degeneration.

ACKNOWLEDGMENTS

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Drs. Jan H. Veldink and Leonard H. van den Berg contributed equally to this work.

This work was supported by Prinses Beatrix Fonds and the Netherlands ALS Foundation. The work leading to this investigation received funding from the European Community’s Seventh Framework Programme (FP7/2007–2013) under the Health Cooperation Programme. Conflict of interest: none declared.

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