Background: Cigarette smoking has been proposed as a risk factor for amyotrophic lateral sclerosis (ALS), but epidemiological studies supporting this hypothesis have been small and mostly retrospective.

Objective: To prospectively examine the relation between smoking and ALS in 5 well-established large cohorts.

Design: Five prospective cohorts with study-specific follow-up ranging from 7 to 28 years.

Setting: Academic research.

Patients: Participants in the Nurses’ Health Study, the Health Professionals Follow-up Study, the Cancer Prevention Study II Nutrition Cohort, the Multiethnic Cohort, and the National Institutes of Health–AARP (formerly known as the American Association of Retired Persons) Diet and Health Study.

Main Outcome Measures: Amyotrophic lateral sclerosis deaths identified through the National Death Index. In the Nurses’ Health Study and the Health Professionals Follow-up Study, confirmed nonfatal incident ALS was also included.

Results: A total of 832 participants with ALS were documented among 562,804 men and 556,276 women. Smokers had a higher risk of ALS than never smokers, with age- and sex-adjusted relative risks of 1.44 (95% confidence interval, 1.23–1.68; P < .001) for former smokers and 1.42 (95% confidence interval, 1.07–1.88; P = .02) for current smokers. Although the risk of ALS was positively associated with pack-years smoked (P < .001), duration of smoking (9% increase for each 10 years of smoking, P = .006), and the number of cigarettes smoked per day (10% increase for each increment of 10 cigarettes smoked per day, P < .001), these associations did not persist when never smokers were excluded. However, among ever smokers, the risk of ALS increased as age at smoking initiation decreased (P = .03).

Conclusions: Results of this large longitudinal study support the hypothesis that cigarette smoking increases the risk of ALS. The potential importance of age at smoking initiation and the lack of a dose response deserve further investigation.

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of whom died of ALS. However, in a 2009 multicenter prospective study in Europe that included 118 participants with ALS, current smokers had 2-fold increased rates of ALS compared with never smokers, with no significant differences by sex.

To better understand cigarette smoking relative to the risk of ALS, we conducted an analysis using 5 large ongoing cohort studies. In this sample, we documented 832 participants with ALS.

METHODS

STUDY POPULATION

The study population comprised participants in the following: the Nurses’ Health Study (NHS), the Health Professionals Follow-up Study (HPFS), the CPS-II Nutrition Cohort, the Multiethnic Cohort (MEC), and the National Institutes of Health–AARP (formerly known as the American Association of Retired Persons) Diet and Health Study (NIH-AARP).

The NIH cohort was established in 1976 when 121 701 female registered nurses from 11 US states, aged 30 to 55 years, responded to a mailed questionnaire about disease history and lifestyle. The HPFS began in 1986 when 51 529 male health professionals (dentists, optometrists, pharmacists, podiatrists, and veterinarians), aged 40 to 75 years, answered a similar mailed questionnaire. Follow-up questionnaires are mailed to the participants in both studies every 2 years to update information on potential risk factors for chronic diseases and to ascertain whether major medical events have occurred.

The CPS-II Nutrition Cohort comprises 86 404 men and 97 786 women, aged 50 to 79 years, from 21 states with populations included in the 1980 United States Census. The MEC study consists of 96 937 men and 118 843 women, aged 45 to 75 years, living in Hawaii and the Los Angeles, Los Angeles County (primarily Los Angeles) and mainly from the following 5 self-reported racial/ethnic groups: African American, Native Hawaiian, and white.

The NHS cohort was established in 1976 when 121 701 female registered nurses from 11 US states, aged 30 to 55 years, responded to a mailed questionnaire about disease history and lifestyle. The HPFS began in 1986 when 51 529 male health professionals (dentists, optometrists, pharmacists, podiatrists, and veterinarians), aged 40 to 75 years, answered a similar mailed questionnaire. Follow-up questionnaires are mailed to the participants in both studies every 2 years to update information on potential risk factors for chronic diseases and to ascertain whether major medical events have occurred.

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DATA ANALYSIS

Each participant contributed person-time of follow-up from the return date of the baseline questionnaire to the date at onset of first ALS symptoms, death from ALS or any other cause, or the end of follow-up, whichever came first. The end of follow-up was June 2004 for the NHS, December 2003 for the HPFS, December 2004 for the CPS-II Nutrition Cohort, December 2002 for the MEC, and December 2005 for the NIH-AARP. Age-specific rates were calculated as the number of ALS cases divided by person-time of follow-up in each age group.

In the NHS and the HPFS, we also documented incident ALS. In each biennial follow-up questionnaire, participants were asked to report a specific list of medically diagnosed conditions (initially not including ALS) and “any other major illness.” Amyotrophic lateral sclerosis was then added to the list of specific conditions in 1992 for the NHS cohort and in 2000 for the HPFS cohort, as well as on each subsequent biennial questionnaire. For all participants who reported a diagnosis of ALS by responding to the open question on major illnesses or in answering the specific question, we requested permission for release of relevant medical records. However, because of the rapidly progressive nature of the disease, many participants with ALS died before we could send the release request for medical records; therefore, the request was sent to the closest family member. After obtaining permission, we asked the treating neurologists to complete a questionnaire to confirm the diagnosis of ALS and the certainty of the diagnosis (definite, probable, or possible) or to send a copy of the medical records. The primary diagnosis was made by a neurologist with experience in ALS diagnosis (G.L.) based on the review of medical records.

We relied on the diagnosis made by the treating neurologist if the information in the medical record was insufficient or could not be obtained. When we were unable to obtain a copy of the medical record or the neurologist’s questionnaire for incident self-reported ALS, we classified the participant as having possible ALS and excluded him or her from the primary analysis.

ASCERTAINMENT OF ALS

Follow-up of ALS in the CPS-II Nutrition Cohort, MEC, and NIH-AARP was through a search of the National Death Index. Vital status of the participants in these studies was determined by automated linkage with the National Death Index. The underlying and contributing causes of death were coded according to the International Classification of Diseases, Ninth Revision. All individuals with code 335.2 (motor neuron disease) listed as the underlying or contributing cause of death were considered to have had ALS. In a previous validation study, it was found that ALS was the primary diagnosis in virtually all instances in which code 335.2 was listed as a cause of death.

In the NHS and the HPFS, we also documented incident ALS. In each biennial follow-up questionnaire, participants were asked to report a specific list of medically diagnosed conditions (initially not including ALS) and “any other major illness.” Amyotrophic lateral sclerosis was then added to the list of specific conditions in 1992 for the NHS cohort and in 2000 for the HPFS cohort, as well as on each subsequent biennial questionnaire. For all participants who reported a diagnosis of ALS by responding to the open question on major illnesses or in answering the specific question, we requested permission for release of relevant medical records. However, because of the rapidly progressive nature of the disease, many participants with ALS died before we could send the release request for medical records; therefore, the request was sent to the closest family member. After obtaining permission, we asked the treating neurologists to complete a questionnaire to confirm the diagnosis of ALS and the certainty of the diagnosis (definite, probable, or possible) or to send a copy of the medical records. The primary diagnosis was made by a neurologist with experience in ALS diagnosis (G.L.) based on the review of medical records.

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There are few established risk factors for ALS. When considering potential confounders of the relation between smoking and ALS, we chose variables strongly associated with smoking for which there is also some evidence of their being risk factors for ALS. In support of these variables being reasonably well measured, each cohort validated them directly or found that they predicted disease. In addition to sex-adjusted RRs, we calculated the RRs for women and men separately. The log RRs from the 5 cohorts were pooled using a random-effects model and were weighted by the inverse of their variances.

Interactions between smoking status and baseline age were explored as multiplicative terms in the Cox proportional hazards models in each cohort, and significance was ascertained using the likelihood ratio test. We performed similar analyses for other potential modifiers such as vitamin E and vitamin C supplement intake in each of the cohorts and sex in the CPS-II Nutrition Cohort, MEC, and NIH-AARP cohorts. To minimize the possibility of including participants who already had symptoms of ALS at the time of completing the baseline questionnaire, we conducted additional analyses that excluded the first 4 years of follow-up.

Most analyses were performed using a commercially available statistical software package (SAS version 9.1; SAS Institute Inc, Cary, North Carolina). The estimation of pooled estimates was calculated using another software package (STATA version 9; StataCorp LP, College Station, Texas).

Table 1 gives the study-specific characteristics and smoking history of the 5 cohorts at baseline. Follow-up time ranged from 9 years in the MEC to 18 years in the HPFS. In total, 832 participants had ALS among 1119080 individuals.
556,276 women, after applying study-specific exclusions. Among those with ALS, 16 (15 in the NIH-AARP and 1 in the HPFS) with missing information about smoking status were excluded from the analyses. P-values for the tests of heterogeneity between studies were calculated using Q statistic.

Table 3. Pooled RRs of ALS by Smoking Category at Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of ALS Cases</th>
<th>Person-years</th>
<th>RR (95% CI)</th>
<th>P Value for Heterogeneity</th>
<th>Overallb</th>
<th>No. of ALS Cases</th>
<th>Person-years</th>
<th>RR (95% CI)</th>
<th>P Value for Heterogeneity</th>
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</thead>
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<td>Never smokers</td>
<td>258</td>
<td>5,280,234</td>
<td>1.0 [Reference]</td>
<td>...</td>
<td>1.0 [Reference]</td>
<td>5,280,234</td>
<td>1.0 [Reference]</td>
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<td>...</td>
</tr>
<tr>
<td>Former smokers</td>
<td>450</td>
<td>5,401,310</td>
<td>1.44 (1.23-1.68)</td>
<td>&lt;.001</td>
<td>.97</td>
<td>1.46 (1.25-1.71)</td>
<td>&lt;.001</td>
<td>.95</td>
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<td>Current smokers</td>
<td>108</td>
<td>1,905,109</td>
<td>1.42 (1.07-1.88)</td>
<td>.02</td>
<td>.26</td>
<td>1.34 (0.99-1.82)</td>
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<tr>
<td>Ever smokers</td>
<td>558</td>
<td>7,314,081</td>
<td>1.42 (1.22-1.66)</td>
<td>&lt;.001</td>
<td>.97</td>
<td>1.43 (1.23-1.66)</td>
<td>&lt;.001</td>
<td>.83</td>
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<td>Pack-years smoked ≤20</td>
<td>221</td>
<td>3,652,575</td>
<td>1.31 (1.07-1.57)</td>
<td>.004</td>
<td>.74</td>
<td>1.31 (1.09-1.57)</td>
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<tr>
<td>21-35</td>
<td>169</td>
<td>1,793,611</td>
<td>1.71 (1.30-2.25)</td>
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<td>.21</td>
<td>1.70 (1.26-2.28)</td>
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<td>&gt;35</td>
<td>152</td>
<td>1,671,689</td>
<td>1.43 (1.13-1.79)</td>
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<td>.37</td>
<td>1.42 (1.10-1.84)</td>
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<td>.27</td>
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<td>P for trend</td>
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<tr>
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<td>Former smokers</td>
<td>300</td>
<td>2,978,458</td>
<td>1.26 (1.03-1.55)</td>
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<td>.98</td>
<td>1.30 (1.06-1.69)</td>
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<tr>
<td>Current smokers</td>
<td>52</td>
<td>595,189</td>
<td>1.35 (0.97-1.87)</td>
<td>.07</td>
<td>.91</td>
<td>1.36 (0.98-1.89)</td>
<td>.07</td>
<td>.87</td>
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<tr>
<td>Ever smokers</td>
<td>352</td>
<td>3,577,576</td>
<td>1.28 (1.04-1.56)</td>
<td>.02</td>
<td>.97</td>
<td>1.31 (1.07-1.61)</td>
<td>.009</td>
<td>.96</td>
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</tr>
<tr>
<td>Pack-years smoked ≤20</td>
<td>110</td>
<td>1,557,353</td>
<td>1.02 (0.79-1.31)</td>
<td>.90</td>
<td>.98</td>
<td>1.03 (0.80-1.34)</td>
<td>.80</td>
<td>.99</td>
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<tr>
<td>21-35</td>
<td>127</td>
<td>927,757</td>
<td>1.80 (1.40-2.31)</td>
<td>&lt;.001</td>
<td>.38</td>
<td>1.84 (1.44-2.36)</td>
<td>&lt;.001</td>
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<tr>
<td>&gt;35</td>
<td>107</td>
<td>1,006,466</td>
<td>1.25 (0.90-1.76)</td>
<td>.20</td>
<td>.25</td>
<td>1.31 (0.91-1.88)</td>
<td>.15</td>
<td>.21</td>
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<td>P for trend</td>
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<td>P for trend, smokers only</td>
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<td>Women</td>
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<tr>
<td>Never smokers</td>
<td>124</td>
<td>3,464,557</td>
<td>1.0 [Reference]</td>
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<td>1.0 [Reference]</td>
<td>3,464,557</td>
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<tr>
<td>Former smokers</td>
<td>150</td>
<td>2,422,652</td>
<td>1.65 (1.27-2.14)</td>
<td>&lt;.001</td>
<td>.34</td>
<td>1.65 (1.29-2.12)</td>
<td>&lt;.001</td>
<td>.35</td>
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<tr>
<td>Current smokers</td>
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<td>1,309,920</td>
<td>1.47 (0.86-2.49)</td>
<td>.16</td>
<td>.05</td>
<td>1.34 (0.79-2.28)</td>
<td>.28</td>
<td>.05</td>
<td></td>
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<tr>
<td>Ever smokers</td>
<td>206</td>
<td>3,736,504</td>
<td>1.56 (1.16-2.08)</td>
<td>.003</td>
<td>.19</td>
<td>1.52 (1.15-2.02)</td>
<td>.004</td>
<td>.22</td>
<td></td>
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<tr>
<td>Pack-years smoked ≤20</td>
<td>111</td>
<td>2,095,223</td>
<td>1.64 (1.19-2.27)</td>
<td>.003</td>
<td>.22</td>
<td>1.62 (1.18-2.21)</td>
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<td>.25</td>
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<td>21-35</td>
<td>42</td>
<td>864,854</td>
<td>1.41 (0.96-2.07)</td>
<td>.08</td>
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<td>1.36 (0.93-1.98)</td>
<td>.11</td>
<td>.40</td>
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<td>&gt;35</td>
<td>45</td>
<td>665,224</td>
<td>1.73 (1.11-2.68)</td>
<td>.02</td>
<td>.24</td>
<td>1.64 (1.04-2.58)</td>
<td>.03</td>
<td>.22</td>
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<td>P for trend, smokers only</td>
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Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; ellipses, not applicable; RR, relative risk.

a Among those with ALS, 16 (15 in the NIH-AARP and 1 in the Health Professionals Follow-up Study) with missing information about smoking status were excluded from the analyses. P-values for the tests of heterogeneity between studies were calculated using Q statistic.

b Also adjusted for sex.

556,276 women, after applying study-specific exclusions. Among those with ALS, 16 (15 in the NIH-AARP and 1 in the HPFS) with missing information about smoking status were excluded from the analyses. The proportion of ever smokers was lowest (42.5%) among women in the MEC study and was highest (69.2%) among men in the MEC study. In each cohort, smokers were similar to nonsmokers in terms of body mass index, physical activity, and education (Table 2). The rates of ALS in the 5 cohorts combined increased with age, were consistently higher in men than women for each age group (Figure 1), and are similar to the age- and sex-specific ALS mortality rates for the United States (Table 1) and Europe. Participants who had ever smoked cigarettes at baseline had an increased risk of ALS compared with never smokers (Table 3). In the age- and sex-adjusted analyses, the pooled RRs were 1.44 (95% CI, 1.23-1.68; P < .001) for former smokers and 1.42 (95% CI, 1.07-1.88; P = .02) for current smokers compared with never smokers. The pooled RRs for smokers were slightly higher in female smokers than in male smokers, but the difference was not significant (P = .40 for interaction). When the data in the first 4 years of follow-up were excluded to minimize the potential influence of latent diseases on smoking reported at baseline, the pooled RRs were almost identical to those as reported earlier (age- and sex-adjusted RR, 1.38; 95% CI, 1.09-1.77; P = .009 for ever smokers compared with never smokers). No significant interactions were found between smoking and the use of vitamin E or vitamin C supplements (P > .05).

In analyses based on pack-years smoked, the RR of ALS was 1.31 for 20 or fewer pack-years smoked, 1.71 for 21 to 35 pack-years, and 1.43 for more than 35 pack-years (Table 3). Despite the fact that ALS risk did not increase monotonically with pack-years smoked, the overall test for linear trend was significant (P = .001). Adjustment for body mass index, education, and physical activity did not materially affect the pooled estimates. The mean number of cigarettes smoked per day and the duration of smoking were positively associated with ALS when examined.
In this prospective study, cigarette smoking was associated with a significantly higher risk of ALS. Significant trends in the risk of ALS were observed with the duration of smoking and the number of cigarettes smoked per day, but these trends were largely driven by the low ALS risk among never smokers. Among individuals who ever smoked, the risk of ALS increased with decreasing age at smoking initiation but not with duration or intensity of smoking.

The strengths of the present study include the prospective design and the many participants with ALS. These cohorts are more likely to be representative of the whole spectrum of patients with ALS, avoiding selection that is likely when patients are recruited in ALS tertiary care centers. One limitation is the use of ALS mortality in the CPS-II Nutrition Cohort, MEC, and NIH-AARP cohorts as a proxy for ALS incidence. However, we assume that mortality is a reasonable surrogate for incidence because the median survival after ALS diagnosis (1.5-3 years) is short. Death certificates have been estimated to accurately identify 70% to 90% of ALS or motor neuron diseases–related deaths; therefore, bias is unlikely unless the underreporting is strongly related to smoking. In addition, the use of mortality could result in inclusion of prevalent ALS at baseline, but sensitivity analyses that excluded the first 4 years of follow-up in each cohort showed similar results. Although the study population was not chosen to be representative of the US population, the ALS mortality rates among participants in these 5 cohorts are comparable to those among the US population of similar age and sex.
line cigarette smoking information was used in the analysis because the questionnaire for the period of this analysis in the MEC and the NIH-AARP was administered only once; therefore, changes in cigarette smoking during the follow-up period were not captured. Although measurement error in BMI, education, or physical activity may result in residual confounding, it is unlikely to explain the strong results reported.

Our results are consistent with recent epidemiologic evidence that links cigarette smoking with an increased risk of ALS. In a population-based case-control study in Washington State, investigators reported an odds ratio of 2 (95% CI, 1.3-3.2) for the broad smoking category of ever smokers compared with never smokers. They also found a significant increase in the risk of ALS among those with more pack-years smoked and longer duration of smoking. In a case-control study in the Netherlands that included 364 cases found odds ratios of 1.7 (95% CI, 1.1-2.6) for current smokers and 1.6 (95% CI, 1.0-2.5) for former smokers compared with never smokers. Among smokers, no dose response for pack-years smoked was observed. In 2004, Weisskopf et al reported that mortality from ALS in the CPS-II Mortality Cohort (the parent cohort for the CPS-II Nutrition Cohort) was 70% higher among female smokers but was not elevated among male smokers (RR, 0.7; 95% CI, 0.5-1.0), indicating a possible sex difference in the determinants of ALS. We did not find significant sex differences in the association between cigarette smoking and ALS. In a 2009 analysis of the multicenter European Prospective Investigation Into Cancer and Nutrition cohort, current smokers had approximately a 2-fold increase in ALS rates compared with never smokers (RR, 1.89; 95% CI, 1.14-3.14), while former smokers had a 50% increased rate (RR, 1.48; 95% CI, 0.94-2.32). The authors also reported a dose response across the number of years spent smoking but not the pack-years smoked.

Several possible mechanisms by which cigarette smoking might influence the risk of ALS have been suggested, including direct neuronal damage from nitric oxide or other components of cigarette smoke (such as residues of pesticides used in tobacco cultivation) or from oxidative stress. Chemicals that are present in cigarette smoke generate free radicals and products of lipid peroxidation, and smokers have a higher turnover of the major antioxidant vitamin C. Exposure to formaldehyde, a by-product of the combustion process of tobacco smoking, was reported in 2008 to be associated with an increased risk of ALS. Inhibition of vascular endothelial growth factor has been postulated as a possible explanation for smoke-related effects on neurons.

On the other hand, the observation that among smokers ALS risk is affected by age at smoking initiation but not by duration or intensity of smoking seems hard to reconcile with a simple toxic effect of tobacco components or additives. Because of the large sample size, it is unlikely that a strong dose-response relation between pack-years smoked and ALS risk would have been missed in our study. Possible explanations for the lack of a biological gradient include the following: (1) smoking is only relevant at a young age, perhaps during adolescence when the body is growing and motor neurons are under additional stress; (2) smoking may act in genetically or otherwise susceptible individuals by triggering an autoimmune or otherwise self-perpetuating neurodegenerative process that then runs its course independently of smoking behavior; (3) long-term heavy-smoking survivors are a selected group with low genetic susceptibility to ALS; or (4) one or more of several hundred chemicals contained in tobacco smoke are neuroprotective and with chronic exposure compensate for the adverse effects of other chemicals. The latter hypothesis may seem far-fetched, but it is indirectly corroborated by the low risk of Parkinson disease among smokers.

Finally, as in all observational studies, confounding by unmeasured factors could explain the findings presented; an association with smoking could reflect a true association with another behavior related to being a smoker.

In summary, in this large longitudinal investigation based on 5 cohorts of US men and women, the risk of ALS was higher for cigarette smokers compared with never smokers. Among smokers, the risk of ALS increased with decreasing age at smoking initiation but was unrelated to smoking duration or intensity. Better understanding of the relation between smoking and ALS may further the discovery of other risk factors and help elucidate the nature of the disease.

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