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Smoking and risk of amyotrophic lateral sclerosis: a pooled analysis of five prospective cohorts

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Abstract

Objective—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. We therefore prospectively examined the relation between smoking and ALS in five well-established large cohorts.

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

Subjects—Participants of the Nurses' Health Study (NHS), the Health Professionals Follow-up Study (HPFS), the Cancer Prevention Study II Nutrition Cohort, the Multiethnic Cohort, and the NIH-American Association of Retired Persons Diet and Health Study.

Main Outcome Measure—ALS deaths identified through the National Death Index. In NHS and HPFS confirmed non-fatal incident ALS was also included.

Results—832 participants with ALS were documented among 562,804 men and 556,276 women. Smokers had a higher risk of ALS than never smokers: age- and sex-adjusted relative risks=1.44 (95% CI: 1.23–1.68; $p<0.0001$) for former smokers, and 1.42 (95% CI: 1.07–1.88; $p=0.016$) for current smokers. Although the risk of ALS was positively associated with pack-years smoked ($p<0.0001$), duration (9% increase for each 10-years of smoking; $p=0.006$) and cigarettes smoked per day (10% increase for 10 cigarettes per day; $p<0.001$), these associations

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did not persist when never smokers were excluded. However, among ever-smokers, risk of ALS increased as age at smoking initiation decreased ($p=0.028$).

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.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of motor neurons affecting more than 5,500 newly diagnosed patients every year in the US.¹ The consequence of ALS is a dramatic, rapid deterioration of motor function.² There is no cure for ALS and the few available treatments have limited efficacy.¹ About 90% of ALS cases are sporadic and of unknown, possibly environmental, etiology.³ Cigarette smoking might contribute to the risk of ALS either by a direct neurotoxic effect on motor neurons or by increasing oxidative stress. Although a recent review suggests smoking can be considered an established risk factor for ALS, there have been relatively few studies and results have been conflicting.⁴ A positive association between smoking and ALS has been reported in some,^{5–7} but not all case-control studies.^{8–13} These discrepancies may in part be explained by small sample sizes and possible survival, selection, and recall bias.^{8–13} Results of previous longitudinal studies, however, have also been conflicting.^{14, 15} In the Cancer Prevention Study II (CPS-II), in analyses including 621 ALS deaths, cigarette smoking was associated with an increased ALS mortality in women, but not in men.¹⁴ The lack of association between smoking and ALS in men was confirmed in a cohort of male construction workers in Sweden, 160 of whom died of ALS.¹⁵ In contrast, in a recent multi-centered prospective study in Europe, including 118 participants with ALS, current smokers had two-fold increased rates of ALS compared to never smokers, with no significant differences by gender.¹⁶

In order to better understand cigarette smoking in relation to the risk of ALS, we have conducted an analysis using five large ongoing cohort studies, in which we documented 832 participants with ALS.

Methods

Study population

The study population comprised participants in the Nurses' Health Study (NHS), the Health Professionals Follow-up Study (HPFS), the Cancer Prevention Study II (CPS-II) Nutrition Cohort, the Multiethnic Cohort (MEC) and the NIH-American Association of Retired Persons Diet and Health Study (AARP-DH).

The NHS cohort was established in 1976 when 121,701 female registered nurses from eleven US states, aged 30 to 55 years, responded to a mailed questionnaire about disease history and lifestyle.¹⁷ The HPFS study 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.¹⁸ Follow-up questionnaires are mailed to the participants of 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 population-based cancer registries who completed a mailed questionnaire in 1992 to investigate the relation between diet and other lifestyles factors and the risk of incident cancer.¹⁹ Similar questionnaires were sent in 1997 and every 2 years afterwards to update exposure information and newly diagnosed diseases. The MEC study consists of 96,937 men

and 118,843 women, aged 45 to 75 years at baseline, living in Hawaii and California (primarily Los Angeles) and mainly from five self-reported racial/ethnic groups: African-American, Japanese-American, Latino, Native Hawaiian and White. From 1993 to 1996, participants entered the cohort by completing a self-administered mailed questionnaire.²⁰ Additional questionnaires were mailed to the participants at 5-year intervals. The AARP-DH study included 340,148 men and 227,021 women aged 50 to 71 years residing in one of six states or two metropolitan areas with high-quality cancer registries.²¹ The participants completed a mailed food frequency questionnaire at baseline in 1995–6. About two thirds of participants completed a supplementary risk factors questionnaire in 1996. Each of the studies included was reviewed and approved by the institutional review board of the institution at which the study was conducted.

Ascertainment of ALS

Follow-up of ALS in the CPS-II Nutrition Cohort, MEC and AARP-DH was through a search of the National Death Index (NDI). Vital status of the participants in these studies was determined by automated linkage with the NDI. The underlying and contributing causes of death were coded according to the 9th revision of the International Classification of Disease (ICD-9). All individuals with ICD-9 code 335.2 (motor neuron disease) listed as either the underlying or contributing cause of death were considered to have had ALS. In a previous validation study, we found that ALS was the primary diagnosis in virtually all instances where code 335.2 was listed as a cause of death.¹⁴ In NHS and 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”. A specific question on a diagnosis of ALS was then added to the list of specific condition sin 1992 for the NHS cohort and 2000 for the HPFS cohort, and on each subsequent biennial questionnaire. For all participants who reported a diagnosis of ALS, either in response to the open question on major illnesses or by answering the specific question, we requested permission for release of relevant medical records. Because of the rapidly progressive nature of the disease, however, many participants with ALS died before we could send the request of release of medical records, and the request was therefore 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, and possible) or to send a copy of the medical records. The primary diagnosis was made by a neurologist with experience in ALS diagnosis (GL) 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 ‘possible ALS’ and excluded him or her from the primary analysis.

Data analysis

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

The analyses were conducted separately in each cohort, using the baseline smoking information. Because of the long follow-up in the NHS, we split the cases and person-time experienced during follow-up into two uncorrelated segments: 1976–1990 and 1990–2004. In accordance with the underlying theory of survival analysis, blocks of person-time in

different time periods are asymptotically uncorrelated, regardless of the extent to which they are derived from the same persons. Thus, pooling the estimates from the 2 time periods is equivalent to using a single time period but takes advantage of the updated exposure assessment in 1990.

Cox proportional hazards regression was used to estimate relative risks (RRs) and 95% confidence intervals for ever-smokers, or former and current smokers, compared with never smokers adjusted for age and sex. To obtain a better age adjustment, we stratified the Cox models by age in single years. Similar analyses were conducted by categories of pack-years smoked (≤ 20 , 21 to 35, more than 35 pack-years). The significance of trends was assessed by modeling the medians of each category as a continuous variable.²² We also conducted analyses using continuous variables for the average number of cigarettes smoked per day, the total number of years smoked and the age at smoking initiation, first including all participants, and then among smokers only.

Multivariate Cox proportional hazards regression was used to adjust for additional potential confounders: body mass index (BMI); physical activity; and education level. There are few established risk factors for ALS. When considering potential confounders of the smoking and ALS relationship we chose variables strongly associated with smoking for which there is also some evidence of being risk factors for ALS. In support of these variables being reasonably well measured, each cohort either validated them directly^{23, 24} or found they predicted disease.^{25–32} In addition to sex-adjusted RRs, we calculated RRs for women and men separately. The log RRs from the 5 cohorts were pooled using a random-effects model and weighted by the inverse of their variances.

Interactions between smoking status and baseline age ($\leq$ median, or $>$ median) were explored as multiplicative terms in the Cox models in each cohort, and significance was ascertained using the likelihood ratio test. We did 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 AARP-DH 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 excluding the first four years of follow-up.

All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC), except for the estimation of pooled estimates, which were calculated using STATA version 9 (StataCorp LP, College Station, TX).

Results

Table 1 shows the study-specific characteristics and smoking history of the 5 cohorts at baseline. Follow-up time ranged from 9 years in MEC to 18 years in HPFS. In total 832 participants had ALS among 562,804 men and 556,276 women, after applying study-specific exclusions. Among those with ALS, 16 (15 in the AARP-DH and one in the HPFS) with missing information of smoking status were excluded from the analyses. The proportion of ever-smokers was lowest among women (42.4%) and highest among men (69.2%) in the MEC study. In each cohort, smokers were similar to nonsmokers in terms of body mass index, physical activity and education level, except that nonsmokers tended to be more physically active in the AARP-DH cohort (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 US^{33, 34} and Europe.³⁵

Participants who had ever smoked cigarettes at baseline had an increased risk of ALS compared to never smokers (Table 3). In the age- and sex-adjusted analysis, the pooled RR was 1.44 (95% CI: 1.23 to 1.68; $p < 0.0001$) for former smokers and 1.42 (95% CI: 1.07 to 1.88; $p = 0.016$) for current smokers compared to never smokers. The pooled RR for smokers were slightly higher in female than in male smokers, but the difference was not significant (p for interaction = 0.40). When the data in the first four years of follow-up were excluded to minimize the potential influence of latent diseases on smoking reported at baseline, the pooled RR were almost identical to those reported above (ever-smokers compared to never smokers: age-, sex-adjusted RR = 1.38 [95% CI: 1.09–1.77; $p = 0.009$]). No significant interactions were found between smoking and use of vitamin E or vitamin C supplements ($p > 0.05$).

In analyses based on pack-years of smoking, the RR of ALS was 1.31 for ≤ 20 pack-years of smoking, 1.71 for 21–35 pack-years, and 1.43 for more than 35 pack-years. In spite of the fact that ALS risk did not increase monotonically with pack-years of smoking, the overall test for linear trend was significant ($p = 0.001$) (Table 3). Adjustment for body mass index, education and physical activity did not materially affect the pooled estimates. Both the number of cigarettes smoked per day and duration of smoking were positively associated with ALS when examined independently, rather than combined into pack-years: RR increased by 10% for each increment of 10-cigarettes smoked per day, and by 9% for each 10-years smoked (Figures 2 and 3). The association between years smoked and ALS was not modified by age at baseline ($p = 0.44$).

Because the significant trends in the analyses on pack-years, average number of cigarettes per day, or duration of smoking presented above could be driven by inclusion of never smokers, we conducted further analyses restricted to ever-smokers. In these analyses the pack-years of smoking was not significantly associated with ALS risk ($p = 0.6$) (Table 3). Similarly, ALS risk was not significantly related to the number of cigarettes per day ($p = 0.36$) or duration of smoking ($p = 0.94$). The only aspect of smoking behavior that remained predictive of ALS risk was age at smoking initiation; a younger age was associated with a higher risk of ALS (pooled RR = 1.11; 95% CI: (1.01–1.22); $p = 0.028$ for each 5 years younger at initiation) (Figure 4).

Discussion

In this prospective study, we observed that cigarette smoking was associated with a significantly higher risk of ALS. Significant trends in the risk of ALS were observed with the years smoked and the number of cigarette smoked per day, but these trends were largely driven by the low ALS risk among never smokers. Among individuals who ever smoked, risk of ALS increased with decreasing age at smoking initiation, but not with duration or intensity of smoking.

The strengths of the current study include the prospective design and the large number of participants with ALS. These cohorts are more likely to be representative of the whole spectrum of ALS patients, avoiding selection that is likely when patients are recruited in ALS tertiary care centers.³⁶ One limitation is the use of ALS mortality in the CPS-II Nutrition Cohort, MEC and AARP-DH studies as a proxy for ALS incidence. We assume, however, that mortality is a reasonable surrogate for incidence, because median survival of ALS after diagnosis (1.5 – 3 years) is relatively short.^{2, 37–39} Death certificates have been estimated to accurately identify 70–90% of ALS or motor neuron diseases related deaths,^{40–43} thus bias is unlikely unless the underreporting is strongly related to smoking. In addition, 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 very

similar results. Although the study population was not chosen to be representative of the US population, the ALS mortality rates among participants in these five cohorts are comparable to those of the US population of similar age and sex.^{33, 34} Baseline cigarette smoking information was used in the analysis as the questionnaire for the period of this analysis in the MEC and the AARP-DH studies was administered only once, therefore changes in cigarette smoking during the follow-up were not captured. While 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 (OR) of 2 (95% CI: 1.3–3.2) for the broad smoking category of ever-smokers compared to never smokers.⁶ They also found a significant increase in risk of ALS among those with more pack-years of smoking and longer duration of smoking. In a case-control study in New England, cigarette smoking was associated with a significant 70% increase in ALS risk.⁵ This study, however, did not find a dose-response across pack-years or years smoked. A case-control study in the Netherlands including 364 cases found an OR 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 to never smokers.⁷ Among smokers, no dose-response for pack-years was observed. More recently, Weisskopf et al reported that mortality from ALS in the CPS-II mortality cohort (the parent cohort for 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]),¹⁴ indicating a possible gender difference in the determinants of ALS. We did not find significant gender differences in the association between cigarette smoking and ALS. In a recent analysis of the multi-centered EPIC cohort, current smokers had about a two-fold increase in ALS rates compared to 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 number of years spent smoking but not pack-years smoked.¹⁶

Several possible mechanisms by which cigarette smoke might influence the risk of ALS have been suggested, including direct neuronal damage from nitric oxide or other components of cigarette smoke,⁴⁴ such as residues of pesticides used in tobacco cultivation,⁴⁵ or oxidative stress. Chemicals that are present in cigarette smoke generate free radicals and products of lipid peroxidation,⁴⁶ and smokers have a higher turnover of the major antioxidant vitamin C.⁴⁷ Exposure to formaldehyde, a by-product of the combustion process of tobacco smoking, was recently reported to be associated with an increased risk of ALS.⁴⁸ Inhibition of vascular endothelial growth factor (VEGF) has also been postulated as a possible explanation for smoke-related effects on neurons.⁴⁹ 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 of smoking and ALS risk would have been missed in our study. Possible explanations for the lack of a biological gradient include: i) smoking is only relevant at a young age, perhaps during adolescence when the body is still growing and motor neurons are under additional stress; ii) 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; iii) long term, heavy smoking survivors are a selected group, with low genetic susceptibility to ALS; and iv) one or more of the several hundred chemicals contained in tobacco smoke is 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 very low risk of Parkinson disease among smokers.^{50, 51} 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 five cohorts of US men and women, we observed that 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. A 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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Fig. 1.

Amyotrophic lateral sclerosis (ALS) rates in US men and women from the Nurses' Health Study (NHS), the Health Professionals Follow-up Study (HPFS), the Cancer Prevention Study II Nutrition Cohort (CPS-II Nutrition Cohort), and the Multiethnic Cohort (MEC) and the NIH-American Association of Retired Persons Diet and Health Study (AARP-DH).

Figure 2.

Study-specific and pooled multivariable relative risk and 95% confidence interval of amyotrophic lateral sclerosis with increment of each 10-cigarettes smoked per day. The black square and horizontal lines correspond to the study-specific multivariable relative risk and 95% confidence interval, respectively. The area of the black square reflects the study weight (inverse of the variance). The diamond represents the pooled multivariable relative risk and 95% confidence interval. The solid vertical line indicates a relative risk of 1.0. No statistical heterogeneity was found among the risk estimates across individual studies (p for heterogeneity = 0.43). Pooled RR = 1.10 (95% CI, 1.05–1.16, $p < 0.0001$).

Figure 3.

Study-specific and pooled multivariable relative risk and 95% confidence interval of amyotrophic lateral sclerosis (ALS) with increment of each 10-years smoked. The black square and horizontal lines correspond to the study-specific multivariable relative risk and 95% confidence interval, respectively. The area of the black square reflects the study weight (inverse of the variance). The diamond represents the pooled multivariable relative risk and 95% confidence interval. The solid vertical line indicates a relative risk of 1.0. No statistical heterogeneity was found among the risk estimates across individual studies (p for heterogeneity = 0.18). Pooled RR = 1.09 (95% CI 1.03–1.16, $p=0.006$).

Figure 4.

Pooled multivariate relative risk and 95% confidence interval of amyotrophic lateral sclerosis for age at smoking initiation. No statistical heterogeneity was found across individual studies (p for heterogeneity >0.5). Relative risks and 95% confidence intervals were 1.61 (1.08–2.39) for initiating smoking before age 16; 1.35 (1.05–1.73) for 16–<20 years; 1.39 (1.06–1.80) for 20–<30 years; and 0.87 (0.54–1.39) for 30+ years. Age and sex adjusted p for trend across ever smokers = 0.028; multivariate adjusted $p = 0.05$. Excludes AARP-DH as data were not available.

characteristics of the cohort studies included in the pooled analysis of smoking and amyotrophic lateral sclerosis risk

Table 1

Study	Follow-up		Baseline Cohort size *	ALS cases	Baseline age range, y	Baseline smoking status (%)		
	Start	End				never	ever	Missing
HPFS	1986	2003	51,436	58	39–78	44.4	51.7	3.9
NHS	1976	2004	121,570	95	29–62	43.4	56.3	0.3
CPS-IIN men	1992	2004	86,382	114	41–93	31.6	67.9	0.6
CPS-IIN women	1992	2004	97,781	85	40–90	53.8	44.9	1.3
MEC men	1993–7	2002	96,937	43	41–78	29.6	69.2	1.2
MEC women	1993–7	2002	118,843	34	42–78	55.5	42.5	2.0
AARP-DH men	1995–6	2005	328,049	285	50–72	29.3	67.3	3.4
AARP-DH women	1995–6	2005	218,082	118	50–72	44.0	53.0	3.0
Total			1,119,080	832				

* Cohort size after applying study-specific exclusions

Table 2

Selected characteristics of smokers and nonsmokers*

	Nonsmokers	Smokers
NHS		
BMI at baseline, mean (kg/m ²)	24.1	23.5
physical activity, mean, (mets/week)	14.0	14.2
HPFS		
BMI at baseline, mean (kg/m ²)	25.3	25.7
physical activity, mean, (mets/week)	21.8	19.7
CPS-II Nutrition Cohort		
Education, %, above high school	65.0	68.3
BMI at baseline, mean (kg/m ²)	25.9	26.0
physical activity, mean, (mets/week)	13.4	13.4
MEC		
Education, %, above high school	56.1	54.6
BMI at baseline, mean (kg/m ²)	25.7	26.2
physical activity, mean, (mets/week)	11.2	11.2
AARP-DH		
Education, %, above high school	64.2	60.5
BMI at baseline, mean (kg/m ²)	27.0	27.1
physical activity, %, ≥3 times/week	47.5	45.5

* age adjusted

Table 3
Pooled relative risks (95% confidence intervals) of amyotrophic lateral sclerosis by smoking category at baseline

	No. of cases	Person-years	RR ^a (95% CI)	p	p for heterogeneity ^c	RR ^b (95% CI)	P	p for heterogeneity ^c
All								
Never smokers	258	5,280,234	1.0 (ref)			1.0 (ref)		
Former smokers	450	5,401,310	1.44 (1.23–1.68)	<0.0001	0.97	1.46 (1.25–1.71)	<0.0001	0.95
Current smokers	108	1,905,109	1.42 (1.07–1.88)	0.016	0.26	1.34 (0.99–1.82)	0.06	0.2
Ever smokers	558	7,314,081	1.42 (1.22–1.66)	<0.0001	0.97	1.43 (1.23–1.66)	<0.0001	0.83
1–20 pack-years	221	3,652,575	1.31 (1.07–1.57)	0.004	0.74	1.31 (1.09–1.57)	0.004	0.77
21–35 pack-years	169	1,793,611	1.71 (1.30–2.25)	<0.0001	0.21	1.70 (1.26–2.28)	<0.0001	0.16
>35 pack-years	152	1,671,689	1.43 (1.13–1.79)	0.002	0.37	1.42 (1.10–1.84)	0.008	0.27
Pack-years:								
P for trend			0.001		0.30	0.004		0.24
P for trend (smokers only)			0.60		0.07	0.60		0.07
Male								
Never smokers	134	1,815,677	1.0 (ref)			1.0 (ref)		
Former smokers	300	2,978,458	1.26 (1.03–1.55)	0.03	0.98	1.30 (1.06–1.89)	0.01	0.99
Current smokers	52	595,189	1.35 (0.97–1.87)	0.07	0.91	1.36 (0.98–1.89)	0.07	0.87
Ever smokers	352	3,577,576	1.28 (1.04–1.56)	0.02	0.97	1.31 (1.07–1.61)	0.009	0.96
1–20 pack-years	110	1,557,353	1.02 (0.79–1.31)	0.90	0.98	1.03 (0.80–1.34)	0.80	0.99
21–35 pack-years	127	928,757	1.80 (1.40–2.31)	<0.0001	0.38	1.84 (1.44–2.36)	<0.0001	0.40
>35 pack-years	107	1,006,466	1.25 (0.90–1.76)	0.20	0.25	1.31 (0.91–1.88)	0.15	0.21
Pack-years:								
P for trend			0.04		0.14	0.03		0.12
P for trend (smokers only)			0.38		0.05	0.24		0.09
Female								
Never smokers	124	3,464,557	1.0 (ref)			1.0 (ref)		
Former smokers	150	2,422,852	1.65 (1.27–2.14)	<0.001	0.34	1.65 (1.29–2.12)	<0.001	0.35
Current smokers	56	1,309,920	1.47 (0.86–2.49)	0.16	0.05	1.34 (0.79–2.28)	0.28	0.05
Ever smokers	206	3,736,504	1.56 (1.16–2.08)	0.003	0.19	1.52 (1.15–2.02)	0.004	0.22

	No. of cases	Person- years	RR ^a (95% CI)	p	p for heterogeneity ^c	RR ^b (95% CI)	P	p for heterogeneity ^c
1–20 pack-years	111	2,095,223	1.64 (1.19–2.27)	0.003	0.22	1.62 (1.18–2.21)	0.003	0.25
21–35 pack-years	42	864,854	1.41 (0.96–2.07)	0.08	0.38	1.36 (0.93–1.98)	0.11	0.40
>35 pack-years	45	665,224	1.73 (1.11–2.68)	0.02	0.24	1.64 (1.04–2.58)	0.03	0.22
Pack-years:								
P for trend			0.08		0.21	0.12		0.19
P for trend, (smokers only)			0.73		0.18	0.07		0.16

^aadjusted for age, sex (for analysis of total)

^badjusted for age, body mass index, physical activity, education level, sex (for analysis of total)

^cp values for the tests of heterogeneity between studies were calculated using the *Q* statistic

RR=relative risk; CI= confidence interval