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Cigarette smoking and completed suicide: results from 3 prospective cohorts of American adults

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Abstract

Background—Prior reports have indicated a potential dose-response relationship between smoking and suicide. However, this relationship is controversial.

Methods—This study evaluated the association between smoking and risk of death from suicide in three large-scale cohorts of U.S. men and women (n=253,033). Suicide were identified from death certificates among 43,816 men enrolled in the Health Professionals Follow-up Study (HPFS) between 1986-2008,116,566 women in the Nurses' Health Study (NHS) between 1976-2008, and 92,651 women in the NHS II between 1989–2007. Information on smoking was obtained at baseline and updated every two years. Relative risks (RRs) of suicide were estimated using Cox proportional hazards regression models. Cohort specific RRs were pooled using random-effects models. Suicide deaths were determined by physician review of death certificates.

Results—A total of 457 deaths from suicide were documented. Compared to never smokers, the pooled multivariate RR (95% confidence interval [CI]) of suicide was 1.15 (0.91–1.45) for former

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smokers and 2.69 (2.11–3.42) for current smokers. A nonmonotonic dose-response relationship was noted between the number of cigarettes smoked per day (CPD) and suicide risk (P_{trend}<.001). Compared to never smokers, the pooled multivariate RR (95% CI) was 2.59 (1.77–3.79) for those with 1–14 CPD, 2.03 (1.39–2.94) for those with 15–24 CPD, and 4.13 (2.96–5.78) for those with ≥25 CPD.

Limitations—Smoking was self-reported and had some degree of measurement error. Participants were not a representative sample of the U.S. population.

Conclusions—Results from three large cohorts suggest a nonmonotonic dose-response association between smoking and suicide risk.

Keywords

suicide; smoking; tobacco; cohort

1. Introduction

Tobacco use is the leading preventable cause of death in the U.S., killing an estimated 443,000 Americans each year and is responsible for approximately one in every five deaths (Ezzati and Lopez 2003; U.S. Department of Health and Human Services 2010; Oza et al. 2011). In many low- and middle-income countries, use of tobacco products is increasing, while it is steadily and slowly decreasing in many high-income countries (World Health Organization, 2008). In 2007, the prevalence of smokers in U.S. adults (except California) was established at 17.9%, with 5.3% of low-intensity (0–9 cigarettes smoked per day (CPD)), 5.4% of moderate-intensity (10–19 CPD), and 7.2% of high-intensity smokers (≥20 CPD) (Pierce et al. 2011).

Suicide is a major cause of death and an important public health problem (Hawton and van Heeringen 2009). In the U.S., suicide is the 10th leading cause of death, with a rate of 11.9 per 100,000 persons in 2010 (Murphy et al.). The rate of smoking and nicotine dependence are significantly higher for subjects with psychiatric disorders (Lasser et al. 2000; Grant et al. 2004; Pulay et al. 2010) and affective disorders are well-known risk factors for suicide or suicidal behaviors (Kessler et al. 2005). Smoking is one of the leading behavioral causes of ongoing morbidity (U.S. Department of Health and Human Services 2010) and serious physical illness might predispose to higher risk of suicide or suicidal behaviors (Hawton and van Heeringen 2009).

Smoking as a risk factor for suicide has been proposed by cohort studies that found a positive association between cigarette smoking and suicide or suicidal behaviors (Hemenway et al. 1993; Tverdal et al. 1993; Doll et al. 1994; Miller et al. 2000a; Miller et al. 2000b; Tanskanen et al. 2000; Breslau et al. 2005; Iwasaki et al. 2005; Yaworski et al. 2011). However, this relationship is controversial and the explanations for this association remain unclear (Hughes 2008). On the other hand, smoking cessation is often associated with a greater likelihood of experiencing withdrawal syndrome symptoms and depression, which might increase risk of suicide (Glassman et al. 1990; Laje et al. 2001). We therefore accessed data from three large U.S. cohorts in which cigarette smoking was assessed every two years to investigate prospectively and over a long follow-up period the association between smoking and quitting smoking and risk of deaths from suicide. The present work represents an extension of a previous brief report in the NHS (Hemenway et al. 1993) and a report based on only 8 years of follow-up in the HPFS (Miller et al. 2000b).

2. Methods

2.1 Study Population

The designs of the Health Professionals Follow up Study (HPFS), Nurses' Health Study (NHS) and Nurses' Health Study-II (NHS II) have been described previously (Ascherio et al. 2001; Colditz and Hankinson 2005). The NHS is a prospective cohort study comprising 121,700 female U.S. registered nurses aged 30 to 55 years in 1976. The HPFS is a prospective cohort study comprising 51,529 male U.S. health professionals aged 40 to 75 years in 1986. The NHS II is a prospective cohort study comprising 116,671 female U.S. registered nurses aged 25 to 42 years in 1989. Participants in all cohorts were followed with biennial questionnaires on lifestyle (including diet every 4 years), medication use, and disease incidence.

To identify a healthy population, participants with diagnoses of cardiovascular disease or cancer at baseline were excluded. After further exclusion of participants with missing information on smoking at baseline, data from 43,816 participants in HPFS (1986–2008), 116,566 in NHS (1976–2008) and 92,651 in NHS II (1989–2007) were available for analysis. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health.

2.2 Assessment of Smoking

Smoking status was assessed at baseline in each cohort and was updated on subsequent biennial questionnaires. The initial cohort questionnaires also asked for age at which regular smoking began, age at quitting, and the usual number of cigarettes smoked per day. The number of cigarettes smoked per day was reported every 2 years by category (1–4, 5–14, 15–24, 25–34, 35–44, ≥45). For smoking status and CPD, the last value was carried forward to replace missing values. Duration of smoking and years since quitting were derived based on information from the initial and subsequent questionnaires and updated during each follow-up cycle, and, therefore, their accuracy is within 2 years. Duration of smoking was calculated as the difference between age at smoking initiation and current age for current smokers, or between age at onset and cessation for former smokers. Years since cessation were obtained for former smokers by deducting the age of quitting smoking from current age. Ages at smoking initiation and cessation were continuous values in the NHS cohort but were collected categorically in NHS II (<15, 15–19, 20–24, 25–29, 30–35 years) and HPFS (<15, 15–19, 20–29, 30–39, 40–49, 50–59, ≥60 years).

2.3 Ascertainment of Death from Suicide

Deaths were identified by next of kin or postal authorities, or by searching the National Death Index. At least 98% of deaths among the study participants were identified (Rich-Edwards et al. 1994). Physicians reviewed death certificates to classify individual causes of death. The end point of this study comprised all death cases of suicide and self-inflicted injuries (*Eighth Revision International Classification of Diseases* [ICD] codes E950 to E959) (US Dept of Health, Education, and Welfare 1963). Suicide might refer to several terminologies, e.g. behavior, ideation, plan, attempt, and completed suicide. In this study, the term “suicide” refer to death or completed suicide and "suicidal behaviors" for nonfatal suicidal thought, ideation, plan, and/or attempt.

2.4 Statistical Analysis

Person-years of follow-up were calculated from the date of return of the baseline questionnaire (1986 for HPFS, 1976 for NHS, and 1989 for NHS II) to the earliest of: date of death from suicide or another cause; end of follow-up (January 1, 2008 for HPFS, June

30, 2008 for NHS and, June 30, 2007 for NHS II); or return date of the last questionnaire received during follow-up. Cox proportional hazards models, stratified on age in months and questionnaire cycle, were used to estimate relative risks (RRs) and 95% confidence intervals (CIs). Linear trends were tested by modeling medians of categories of exposure. Analyses were performed separately in each cohort and cohort-specific estimates were pooled using random-effect summaries.

Clinical relevance guided the choice of covariates (Hernan et al. 2002). The multivariate models were adjusted for time varying confounders using simple updating information at each 2-year and 4-year questionnaire cycle, including high alcohol consumption (≥30 g/day, <30 g/day), caffeinated coffee consumption (continuous, cup/d), body-mass index (<25.0, 25.0 to 29.9, ≥30.0 kg/m^2), physical activity (quintiles), marital status (married/partnered or widowed/separated/divorced/single), and reported regular use of antidepressants (yes or no) and minor tranquilizers such as benzodiazepines (yes or no). In NHS II, hormonal status (post-menopausal with or without hormonal therapy, pre-menopausal or never used hormonal therapy) was also included. Sensitivity analyses including factors that can mediate the effects of smoking, such as self-reported high blood pressure, myocardial infarction or angina, stroke, and cancer (all yes/no) were preformed. All analyses were performed with SAS software, version 9.2 (SAS Institute Inc., 2003). All *P* values reported are 2-sided.

3. Results

Participant characteristics according to smoking status are presented in Table 1. At baseline, prevalence of current smokers was 32% for NHS, 12.8% for NHS II, and 10.3% for HPFS. Compared to never smokers, current smokers were more likely to consume more alcohol and caffeine, reported a higher prevalence of regular use of antidepressants and minor tranquilizers, and a lower prevalence of married/partnership status.

A total of 457 deaths from suicide were documented among the 253,033 participants: 221 in NHS (rate=6.3/100,000 person-years), 71 in NHS II (rate=4.3/100,000), and 165 in HPFS (rate=19.2/100,000). After multivariate adjustment, current smoking was associated with a higher suicide risk in all cohorts (Table 2). Compared to never smokers, the pooled multivariate RR of suicide was 1.15 (95% CI, 0.91–1.45) for former smokers and 2.69 (95% CI, 2.11, 3.42) for current smoker. The risk of suicide was higher as the number of CPD increased (P_{trend}<.001), and was the highest among those who smoked ≥25 CPD (pooled multivariate RR=4.13; 95% CI, 2.96–5.78). Among former smokers, the risk of suicide was not associated with the number of CPD in the past (data not shown). Compared to those who smoked for less than 10 years, risks of suicide were not statistically significant among those who smoked for 10–19 years or ≥20 years. Age at the start of smoking was not associated with risk of suicide. Smoking cessation was not associated with risk of suicide (P_{trend}=0.62), compared to never smokers. The pooled multivariate RR of suicide was 1.45 (95% CI, 0.93–2.26) for those who had quit for ≤5 years and 1.10 (95% CI, 0.86-1.42) for those who had quit for >5 years.

The findings remained essentially unchanged after further adjustment for comorbid diseases (hypertension, cardiovascular disease, or cancer), other socio-economic variables (education, spouse's education, retirement), or four categories of alcohol intake (<5g/day, 5 to <15g/day, 15 to <30g/day, ≥30g/day) (data not shown). In addition, no significant interactions were found between ever smoking status (yes/no) and alcohol use (yes/no) (all $P_{interaction}$ ≥0.18), and reported regular use of antidepressants or minor tranquilizers (yes/no) (all $P_{interaction}$≥0.29).

4. Discussion

In these three large prospective cohorts of U.S. men and women, results indicated that suicide risk was higher among current smokers, and it increased in a nonmonotonic dose-dependent manner with increasing number of CPD. As compared with never smokers, the pooled multivariate RR of suicide was 2.7 times higher among current smokers, and was 4 times higher among those who smoked ≥25 CPD. The lack of association between duration of smoking or age at the start of smoking and suicide suggests that recent smoking behavior, especially the frequency, is associated with suicide risk.

The current study results are consistent with previous cohort results in which a higher risk of suicide or suicidal behavior was observed among current smokers. (Hemenway et al. 1993; Tverdal et al. 1993; Doll et al. 1994; Miller et al. 2000a; Miller et al. 2000b; Tanskanen et al. 2000; Breslau et al. 2005; Iwasaki et al. 2005; Yaworski et al. 2011). The present study also confirms results of a recent meta-analysis of prospective cohort studies (Li et al. 2012). In the present study, current daily smoking, but not past smoking, was significantly associated with 2.7 times higher high risk of suicide. However, current smoking was associated with 1.8 times higher risk of suicide (95% CI=1.50–2.19) in the recent meta-analysis (Li et al. 2012). Results of the current study suggest a nonmonotonic dose-response relationship between the number of CPD and suicide risk, with a greater than fourfold increase in risk among heavy smokers (≥25 CPD). Likewise, Tanskanen et al. (2000) noted a dose-response relationship between the number of CPD and suicide risk among 36,527 men and women with mean follow-up of 14.4-year. Compared with non-smokers, adjusted RR of suicide death was about two times higher for light/moderate smokers (1–20 CPD) and over three times higher for heavy smokers (≥21 CPD) after adjustment for several confounders, especially alcohol consumption, symptoms of depressed mood, stress and anxiety, and psychotropic medication (Tanskanen et al. 2000)

Lower monoamine oxidase (MAO) activity (Whitfield et al. 2000) and serotonin function (Malone et al. 2003) in smokers compared to non-smokers has been proposed as a biological mechanism for the role of smoking in suicide. Deficits in serotonergic function have been associated with an increased hostility, impulsive/aggressive behaviors and suicide (Kamali et al. 2001). A deficiency of central monoamines is one of the features of depression, (Belmaker and Agam 2008) and several antidepressant drugs are designed to increase monoaminergic transmission. However, it has also been suggested that smoking might have antidepressant properties, (Balfour and Ridley 2000) a hypothesis that could explain reduced symptoms of depression noted with the use of nicotine patches among non-smoking depressed patients (Salin-Pascual et al. 1996). Malone et al. (2003) suggested that lower serotonergic function predisposes to smoking habit and psychiatric disorders, and a further depletion of serotonin by smoking after the onset of a depressive disorder, may enhance the risk of aggressive and suicidal behaviors.

Some studies have found that the significant associations observed between smoking and suicide persist after controlling for confounders such as psychiatric disorders (e.g. depression, anxiety), (Tanskanen et al. 2000; Breslau et al. 2005; Yaworski et al. 2011) but other have not (Hemmingsson and Kriebel 2003; Kessler et al. 2007; Boden et al. 2008). However, two of these studies were cross-sectional (Kessler et al. 2007; Yaworski et al. 2011) and most of the prospective cohorts did not adjust for psychiatric disorders (Hemenway et al. 1993; Tverdal et al. 1993; Doll et al. 1994; Leistikow et al. 2000; Miller et al. 2000a; Miller et al. 2000b; Iwasaki et al. 2005). Even if several cohort studies have found a positive monotonic association between cigarette smoking and suicide or suicidal behavior, smoking was assessed only at the cohort inception and not updated during the follow-up. The relationship between smoking and depression has been extensively studied,

but still remains equivocal (Glassman 1993; Covey et al. 1998). According to a twin study, the association between smoking and depression is not causal but arises largely from other factors that predispose to both smoking and depression (Kendler et al. 1993). The relationship between smoking and suicide is complicated by the fact that several suicide risk factors (e.g. depression, impulsivity-aggressiveness, alcohol consumption, poor physical health and disabilities, etc.) are more common among current smokers than among those who have never smoked (Degenhardt and Hall 2001; Ezzati and Lopez 2003; Munafo et al. 2007; Kahler et al. 2009). In the current study, information on smoking behavior was updated every two years, so that it could estimate more accurately the pack-years of smoking and time since quitting. Further, this study allowed to adjust for several potential confounders, including alcohol consumption, caffeine intake, and medical history, using updated and validated information.

A limitation of this study is that although information about some risk factors for suicide were avalaible, information about other risk/preventive factors were lacking. Indeed, this study has a lack information on mental illness (e.g., specific diagnoses, severity), previous suicide attempts, substance abuse/dependence, alcohol abuse/dependence (a distinct variable from alcohol intake itself), firearm availability, sexual orientation, impulsivity-aggressiveness, emotional state (such as hopelessness or anhedonia), social and family support, and spirituality or beliefs (incuding moral objections to suicide) (Nock et al. 2008; Hawton and van Heeringen 2009). Nevertheless, even if complete and detailed information on all the relevant factors were available, the potential confounding is very laborious, because of the complex and reciprocal relation between smoking behavior, psychosocial stress, and mental health. Thus, neither this nor previous investigations can determine causality. Some insight on causality could perhaps be derived by investigating whether trends in smoking behavior at the population level are correlated with opposite trends in suicide rates. Finally, because the participants were predominantly non-Hispanic white health professionals, the generalizability of the observed associations may be limited to similar populations.

In summary, in this large longitudinal study with updated assessment of smoking behavior over a period of decades, results suggest a nonmonotonic dose-response association between smoking and risk of suicide. Heavy current smokers were four times more likely to commit suicide than non-smokers while time since quitting smoking was not associated with suicide risk.

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Table 1

Baseline characteristics of study participants by smoking status[a]

	Smoking status								
	Women (NHS, 1976–2008)			Women (NHS II, 1989–2007)			Men (HPFS, 1986–2008)		
	Never (n=50,897)	Former (n=27,065)	Current (n=38,604)	Never (n=60,932)	Former (n=19,835)	Current (n=11,884)	Never (n=20,911)	Former (n=18,384)	Current (n=4,521)
Age,y	42.7 (7.4)	43.0 (7.1)	42.8 (7.1)	34.3 (4.7)	34.7 (4.4)	34.5 (4.6)	52.6 (9.6)	55.3 (9.5)	53.9 (9.1)
Married/Partnership (%)	94.1	93.7	91.1	79.5	79.7	67.7	91.3	91.8	85.3
Current menopausal hormones (%)	6.1	6.7	6.8	3.6	3.6	4.6	na	na	na
Minor tranquilizers (%)	3.0	3.9	4.2	1.3	1.9	2.7	0.6	0.9	1.4
Antidepressants (%)	5.6	6.6	7.5	12.7	16.9	20.9	0.9	1.1	1.6
BMI (%)[b]									
< 25 kg/m^2	68.4	70.5	75.6	70.6	70.3	69.3	51.5	45.3	48.7
25–29.9 kg/m^2	21.3	19.8	17.6	18.2	18.7	19.1	41.6	46.0	43.9
≥ 30 kg/m^2	9.3	8.7	5.9	11.2	11.0	11.6	6.9	8.7	7.3
Diet intake[c]									
Caffeinated coffee, cups/day[d]	1.4 (1.8)	1.8 (1.9)	2.2 (2.2)	0.9 (1.3)	1.6 (1.5)	2.2 (1.9)	1.0 (1.4)	1.5 (1.6)	2.1 (1.9)
Caffeine, mg/day[e]	256 (260)	303 (278)	352 (321)	197 (190)	278 (214)	384 (257)	181 (202)	252 (234)	337 (274)
Alcohol intake, g/day	4.0 (7.8)	7.5 (10.6)	8.7 (12.9)	2.3 (4.8)	4.3 (6.9)	5.0 (8.9)	8.0 (12.1)	13.7 (16.5)	17.4 (20.2)
≥30 g/day (%)	1.7	4.0	6.7	0.5	1.5	2.9	6.2	14.5	24.1

Abbreviations: HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study.

[a] Values are reported as mean (SD) unless otherwise indicated. Means and percentages are standardized to the age distribution of the study population. Coffee and caffeine consumption were computed as the cumulative average of intake.

[b] The body-mass index is the weight in kilograms divided by the square of the height in meter.

[c] Information on diet was obtained in 1980 for the NHS, 1991 for the NHS II, and 1986 for the HPFS.

[d] One cup= 8 oz or 237 ml.

[e] Caffeine was calculated from coffee and non-coffee sources (tea, caffeinated soft drink, chocolate).

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Table 2

Age- and multivariate-adjusted relative risks (95% CI) of suicide by smoking status[a]

	Men (HPFS, 1986–2008)			Women (NHS, 1976–2008)			Women (NHS II, 1989–2007)			Pooled results[d]
Smoking Variables	**Cases/Pers.- years**	**Age-adjusted[b]**	**Multivariate[c]**	**Cases/Pers.-years**	**Age-adjusted[b]**	**Multivariate[c]**	**Cases/Pers.-years**	**Age-adjusted[b]**	**Multivariate[c]**	**Multivariate[c]**
Smoking status										
Never	63/416,827	1.00	1.00	66/1,522,797	1.00	1.00	32/1,084,429	1.00	1.00	**1.00**
Former smoker	68/392,099	1.09 (0.77–1.54)	1.09 (0.76–1.56)	57/1,258,900	1.09 (0.77–1.56)	1.18 (0.83–1.69)	18/399–971	1.43 (0.80–2.55)	1.21 (0.67–2.18)	**1.15 (0.91–1.45)**
Current smoker	34/61,462	4.38 (2.85–6.74)	3.00 (1.90, 4.76)	98/708,260	2.93 (2.13–4.03)	2.70 (1.95–3.72)	21/177,080	4.20 (2.42–7.30)	2.24 (1.25–4.02)	**2.69 (2.11–3.42**)
Cigarettes smoked per day (CPD) in current vs. never smokers										
Never	63/416,827	1.00	1.00	66/1,522,797	1.00	1.00	32/1,084,429	1.00	1.00	**1.00**
1–14 CPD	9/16,712	4.43 (2.13–9.19)	3.67 (1.70–7.91)	21/205,058	2.25 (1.37–3.70)	2.32 (1.41–3.82)	6/63,594	3.44 (1.44–8.22)	2.30 (0.94–5.64)	**2.59 (1.77–3.79**)
15–24 CPD	8/17,744	3.31 (1.54–7.11)	2.24 (0.99–5.06)	25/270,509	1.92 (1.20–3.07)	1.94 (1.20–3.11)	6/60,413	3.76 (1.57–9.01	2.12 (0.85–5.25)	**2.03 (1.39–2.94)**
≥25 CPD	12/17,386	6.47 (3.34–12.5)	4.62 (2.19–9.74)	45/195,980	4.71 (3.19–6.95)	4.11 (2.74–6.14)	5/27,270	7.07 (2.74–18.2)	3.54 (1.31–9.57)	**4.13 (2.96–5.78)**
P_{trend}		<.001	<.001		<.001	<.001		<.001	0.006	**<.001**
Duration of smoking among former and current smokers										
<10 years	15/109,907	1.00	1.00	14/305,567	1.00	1.00	5/73,892	1.00	1.00	**1.00**
10–19 years	10/100,018	0.71 (0.32–1.61)	0.68 (0.29–1.57)	32/432,833	1.55 (0.82–2.91)	1.47 (0.78–2.76)	12/293,143	0.60 (0.21–1.70)	0.54 (0.19–1.53)	**0.89 (0.47–1.68)**
≥20 years	63/215,211	2.06 (1.15–3.68)	1.69 (0.92–3.12)	105/1,173,711	1.90 (1.07–3.36)	1.73 (0.97–3.08)	19/197,263	1.14 (0.42–3.07)	0.68 (0.25–1.87)	**1.45 (0.90–2.31)**
P_{trend}		0.002	0.03		0.03	0.06		0.34	0.78	**0.01**
Age started smoking among former and current smoker										
≥20 years	11/23,274	1.00	1.00	36/281,251	1.00	1.00	7/49,414	1.00	1.00	**1.00**
<20 years	13/24,318	1.26 (0.52–3.05)	1.94 (0.61–6.18)	53/378,017	1.11 (0.72–1.71)	1.18 (0.76–1.82)	8/97,370	0.63 (0.23–1.74)	0.49 (0.17–1.41)	**1.06 (0.58–1.95)**
Years since quitting in former vs. never Smokers										
Never	63/416,653	1.00	1.00	66/1,522,797	1.00	1.00	32/1,084,429	1.00	1.00	**1.00**
≤5 years	9/41,289	1.69 (0.83–3.43)	1.59 (0.75–3.35)	12/199,237	1.30 (0.70–2.40)	1.48 (0.79–2.74)	3/73,568	1.52 (0.46–4.97)	1.08 (0.33–3.57)	**1.45 (0.93–2.26)**
>5 years	55/340,696	0.98 (0.68–1.42)	1.05 (0.72–1.53)	40/992,857	1.00 (0.67–1.48)	1.13 (0.76–1.68)	14/319,511	1.34 (0.71–2.52)	1.21 (0.64–2.30)	**1.10 (0.86–1.42)**
P_{trend}		0.30	0.46		0.58	0.39		0.77	0.27	**0.62**

Abbreviations: CI, confidence interval; CPD, cigarettes smoked per day; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; RR, relative risk.

[a] Cases of suicide were codes E950 to E959 according the *Eight Revision InternationalClassification of Diseases (ICD)*.

[b] Adjusted for age (continuous) and time interval.

[c] Further adjusted for high alcohol consumption (≥30 g/d, yes or no), body-mass index (<25, 25–29.9, ≥30 kg/m^2), physical activity (quintiles), cups of caffeinated coffee (continuous), marital status (married/partnership or widowed/separated/divorced/single), and reported regular use of minor tranquilizers (yes or no), and antidepressants (yes or no). For women of NHS2, multivariate model was further adjusted for hormonal status (post-menopausal without or with hormonal therapy, pre-menopausal or never used hormonal therapy).

[d] Results from multivariate models were combined using random-effect model.