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Coffee, caffeine, and risk of completed suicide: results from 3 prospective cohorts of American adults

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Abstract

Objective—To evaluate the association between coffee and caffeine consumption and suicide risk in three large-scale cohorts of U.S. men and women.

Methods—We accessed data of 43,599 men enrolled in the Health Professionals Follow-up Study (HPFS, 1988–2008), 73,820 women in the Nurses' Health Study (NHS, 1992–2008), and 91,005 women in the NHS II (1993–2007). Consumption of caffeine, coffee, and decaffeinated coffee, was assessed every four years by validated food-frequency questionnaires. Deaths from suicide were determined by physician review of death certificates. Multivariate adjusted relative risks (RRs) were estimated with Cox proportional hazard models. Cohort specific RRs were pooled using random-effect models.

Results—We documented 277 deaths from suicide. Compared to those consuming ≤1 cup/week of caffeinated coffee (≤8 oz/237 ml), the pooled multivariate RR (95% confidence interval [CI]) of suicide was 0.55 (0.38–0.78) for those consuming 2–3 cups/day and 0.47 (0.27–0.81) for those consuming ≥4 cups/day (*P* trend <0.001). The pooled multivariate RR (95% CI) for suicide was 0.75 (0.63–0.90) for each increment of 2 cups/day of caffeinated coffee and 0.77 (0.63–0.93) for each increment of 300 mg/day of caffeine.

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Conflict of interest statement
The authors have no conflict of interest to declare.

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Conclusions—These results from three large cohorts support an association between caffeine consumption and lower risk of suicide.

Keywords

coffee; caffeine; suicide; cohorts; food-frequency questionnaires

Introduction

Caffeine is a widely used psychostimulant that at low doses reduces fatigue and improves vigilance and locomotor performance (Fredholm et al. 1999; Haskell et al. 2005). The effects of caffeine in the central nervous system are mediated by adenosine receptor antagonism, and include the accelerated turnover of several monoamine neurotransmitters, including serotonin and dopamine, which are involved in depression (Fredholm et al. 1999). These pharmacological actions suggest that caffeine could have antidepressant effects, a hypothesis supported by the observation, in epidemiological studies, that risk of depression (Lucas et al. 2011; Ruusunen et al. 2010) and suicide (Kawachi et al. 1996; Klatsky et al. 1993) is lower in a dose-dependent manner with increasing consumption of caffeinated coffee. An exception is the J-shaped relation between coffee and suicide risk noted in one study where the highest suicide rate was in individuals consuming 8 or more cups of coffee daily (Tanskanen et al. 2000). Previous investigations relied on a single assessment of coffee consumption to predict suicide risk over a long follow-up period, and did not ascertain decaffeinated coffee consumption without which it is difficult to isolate the role of caffeine. We therefore accessed data from three large U.S. cohorts in which consumption of caffeinated and non-caffeinated beverages was assessed every four years to investigate coffee and caffeine consumption and suicide risk.

Subjects and methods

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, we excluded participants with diagnoses of cardiovascular disease or cancer at baseline. The main analyses in the present report use 1992 as the baseline for NHS because a previous report has been published on coffee and suicide risk between 1980 and 1990 (Kawachi et al. 1996). After exclusions, data from 43,599 HPFS, 73,820 NHS and 91,005 NHS II participants 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.

Assessment of exposure

In 1980, NHS participants reported their usual food and beverage intake during the previous year on a 61-item food-frequency questionnaire. In 1984, 1986, 1990, 1994, 1998, and 2002, similar but expanded 131-item questionnaire were sent to these participants. Similar expanded questionnaires were administered to HPFS participants in 1986, 1990, 1994, 1998, and 2002, and to NHS II participants in 1991, 1995, 1999, and 2003. The questionnaires included coffee ("coffee with caffeine" and "decaffeinated coffee"), tea ("nonherbal tea"), carbonated soft drinks (with or without caffeine), and chocolate. Hereinafter, coffee means caffeinated coffee. Each item on the questionnaire referred to a specified amount (e.g., 1 cup for coffee, decaffeinated coffee and tea, 1 glass or can for soft drinks, 1 bar or packet for chocolate) and 9 response categories ranging from never to 6 or more per day. Intakes of nutrients and caffeine were calculated, as described elsewhere (Willett et al. 1985), primarily using concurrent U.S. Department of Agriculture food composition data. In these calculations, we assumed that the caffeine content was 137 mg per cup of coffee (1 cup = 8 oz/237ml), 47 mg per cup of tea, 46 mg per can of soft drink, and 7 mg per serving of chocolate. The food-frequency questionnaires have been evaluated in detail with regard to reproducibility and validity (Salvini et al. 1989; Willett 1998; Willett et al. 1985). Correlations between self-reported coffee intake according to the food-frequency questionnaires and consumption during the 2 or 4 weeks of diet records in both men (r=0.93) (Feskanich et al. 1993) and women (r=0.78) were high (Salvini et al. 1989).

Case ascertainment

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 our study comprised all cases of suicide and self-inflicted injuries (*Eighth Revision International Classification of Diseases* [ICD] codes E950 to E959) (US Dept of Health 1965).

Statistical analysis

Person-years of follow-up were calculated from the date of return of the baseline follow-up questionnaire (1988 for HPFS, 1992 for NHS, and 1993 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]. To account for changes over time and reduce random measurement error, we used the cumulative average of exposure intake from all the available questionnaires. To minimize reverse causation (effect of mental health on coffee consumption) we allowed a 2-year interval between assessment of intake and the start of a follow-up cycle (Hu et al. 1999). For example, in NHS the cumulative average of coffee intake using questionnaires from 1980 through 1990 was used to predict suicide in 1992 to1994 and 1994 to 1996 while intakes

from 1980 through 1994 were used to predict suicide in 1996 to 1998 and in 1998 to 2000, and so on. In sensitivity analyses, a minimum of 4-year latency of exposure was applied. Similar analyses were conducted for categories of caffeine, non-coffee sources of caffeine, and decaffeinated coffee consumption. When a questionnaire was missing, the cumulative average of exposure was based on the previous questionnaires and a missing indicator variable was included in the models. To test for linear trends we modeled 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). In the multivariate analysis, we simultaneously controlled for potential confounders using updated information at each 2-year questionnaire cycle, including smoking status (never smoked, past, currently smoke 1 to 14, 15 to 24, or ≥25 cig./day), high alcohol consumption (≥30 g/day, <30 g/day), body-mass index (<25.0, 25.0 to 29.9, ≥30.0 kg/m^2), physical activity (quintiles), marital status (married/partnered, 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 coffee, such as self-reported high blood pressure, myocardial infarction or angina, stroke, diabetes, and cancer (all yes/no) were preformed. Since caffeine half-life is reduced by 30–50% in smokers and doubled in women taking oral contraceptives or other exogenous estrogens (Fredholm et al. 1999), we examined effect modification by these factors of the caffeine/coffee and suicide associations. All analyses were performed with SAS software, version 9.2 (SAS Institute Inc., 2003). All *P* values reported are 2-sided.

Results

Participant characteristics according to categories of coffee are presented in Table 1. Compared with those with least frequent consumption of coffee (≤1 cup/week), regular coffee drinkers (≥4 cups/day) were more likely to be current smokers and to consume more alcohol, and reported lower prevalence of married/partnership status. In the most recent measure of diet before baseline, mean daily caffeine consumption was 218 mg for NHS, 169 mg for NHS II, and 186 mg for HPFS. Contribution of coffee to total caffeine consumption was 80% for NHS, 71% for NHS II, and 79% for HPFS.

We documented 277 deaths from suicide among the 208,424 participants, 47 in NHS (rate=4.2/100,000 person-years), 66 in NHS II (rate=5.3/100,000), and 164 in HPFS (rate=20.6/100,000). Adjustment for smoking had substantial impact on the relationship between caffeinated coffee (Table 2) and caffeine (Table 3) consumption and suicide risk. Trend toward a lower suicide risk became significant after adjustment for smoking in the three cohorts, mainly reflecting negative confounding by smoking status. Further adjustment for the other variables in the multivariate model had a mild confounding effect. After multivariate adjustment, higher coffee consumption was associated with a lower suicide risk in all cohorts (Table 2). Compared to those consuming ≤1 cup of coffee per week, the pooled multivariate RR of suicide was 0.55 (95% CI: 0.38, 0.78) for those consuming 2 to 3

cups per day, and 0.47 (95% CI: 0.27, 0.81; *P* for trend<0.001) for those consuming ≥4 cups per day. For each increment of 2 cups of coffee per day, the RR for suicide was 0.75 (95% CI: 0.63 to 0.90). Compared to those in the lowest (<100 mg/day) category of caffeine intake, the pooled multivariate RR of suicide was 0.54 (95% CI: 0.30, 0.94) for those with intake between 400 to 550 mg/day and 0.63 (95% CI: 0.39, 1.04; *P* for trend=0.005) for those with intake ≥550 mg/day (Table 3). For each increment of 300 mg of caffeine per day, the pooled multivariate RR for suicide was 0.77 (95% CI: 0.63, 0.93). Results were similar when NHS follow-up started in 1982 (i.e., including suicide cases in a previous paper) (Kawachi et al. 1996).

Sensitivity analyses, i.e. using a latency of 4-year minimum, did not change substantially the multivariate model results. Findings remained essentially unchanged after further adjustment for comorbid diseases (hypertension, diabetes, cardiovascular disease, or cancer), other socioeconomic variables for women (education, husband's education, retirement), or four categories of alcohol intake (<5g/day, 5 to 15g/day, 15 to 30g/day, ≥30g/day) (data not shown). Decaffeinated coffee (Table 4) or tea consumption was not associated with suicide risk (data not shown). Adjustment for smoking had no effect on the relationship between decaffeinated coffee and suicide risk. After further adjustment for cup of caffeinated coffee and other covariates, risk of suicide was not statistically significant with higher consumption of decaffeinated coffee.

The effect of coffee consumption on suicide risk was not modified by smoking status (current/not current) (all *P*≥0.16), alcohol use (yes/no) (all *P*≥0.54), or current menopausal hormone use (yes/no) (all *P*≥0.41).

Discussion

In these three large prospective cohorts of U.S. men and women, we observed that suicide risk, which was similar to that reported in age- and gender-specific U.S. mortality statistics (Rockett et al. 2010), decreased in a dose-dependent manner with increasing consumption of coffee. As compared with non-coffee drinkers, the pooled multivariate RR of suicide was 45% lower among individuals who consumed 2–3 cups of coffee per day, and 53% lower among individual consuming ≥4 cups of coffee per day. The lack of association between decaffeinated coffee and suicide risk suggests that caffeine, rather than other coffee components, contributes to this association. However, consumption of decaffeinated coffee was low and we cannot exclude the possibility that an inverse association with suicide risk could exist for higher consumption.

After searching the English-language medical literature for articles published before February 2012, we identified only three cohort studies that have examined the association between coffee/caffeine consumption and suicide. Lower suicide risk among coffee drinkers was first reported in the Northern California Kaiser Permanente study, a longitudinal investigation of over 120,000 individuals who were followed for an average of 8 years (Klatsky et al. 1993). Suicide risk decreased monotonically with increasing coffee consumption, and was 80% lower in drinkers of >6 cups (question did not specify caffeinated coffee) per day as compared to nondrinkers. Similarly suicide risk was 72%

lower among women in NHS who drank ≥4 cups of caffeinated coffee per day as compared to non-drinkers (decaffeinated coffee was not part of the analysis) during the first 10 years of follow-up (Kawachi et al. 1996). Finally, a J-shaped association was noted between daily coffee drinking and suicide risk in a Finnish population based study comprising over 43,000 individuals who were followed for an average of 14.6 years (Tanskanen et al. 2000). Compared to those drinking ≤1 cup of coffee daily, suicide risk was lower for moderate coffee consumption (2–3 cups/day up to 6–7 cups/day), but increased with higher consumption (8–9 and ≥10 cups/day). The increased suicide risk among heavy coffee drinkers was significant in analyses adjusted for smoking and other potential risk factors for suicide. The increased risk among heavy coffee drinkers could not be confirmed in our cohorts because only 1.9 to 2.8% of participants drank ≥6 cups of coffee daily. Because individuals with mental illness may self-medicate with caffeine (Greden et al. 1978; James and Crosbie 1987), it is possible that persons with more severe forms of depression or other mental illness used very high doses of coffee as a form of self-medication that was, nevertheless, insufficient to improve mood or alleviate dysphoria.

In our study, suicide risk was no further decrease in the highest level of caffeine intake, which might suggest that results for caffeine intake are less convincing than the results for coffee intake. It is possible that caffeine intake results may be affected by the contribution of non-coffee sources of caffeine (20% for NHS, 29% for NHS II, and 21% for HPFS). Biased RR estimates may also result from error in assessing caffeine consumption. Overall, these results suggest that there is little further benefit for consumption above 2–3 cups/day or 400 mg of caffeine/day. Therefore, the continuous estimate should be interpreted with caution.

The results of our study corroborate a lower suicide risk among coffee drinkers, and identify caffeine as the most likely candidate of any putative protective effect of coffee. Although the lack of association between tea and suicide risk seems to contradict this explanation, caffeine intake from tea may have been too low for a measurable effect on suicide risk among participants in our cohorts. However, our study has limited ability to distinguish between caffeine and other components of coffee, and results for decaffeinated coffee should be interpreted with caution. For those who consumed ≥2 cups/d of decaffeinated coffee, the wide confidence interval included both the null value and the RR seen for caffeinated coffee (≥2 cups/d). To avoid contamination by caffeinated coffee consumption, a more rigorous analysis of decaffeinated coffee relationship with suicide risk would require the exclusion of subjects drinking more often caffeinated coffee (e.g. ≥1 cup/d). However, we did not have enough cases and power to perform such analyses.

Unlike previous investigations, we had multiple assessments of coffee and caffeine intake to obtain a cumulative average of consumption, thus reducing random error and accounting for changes in consumption over time. This study also has limitations and the results should thus be interpreted with caution. First and foremost, because of the observational design, neither this nor previous investigations can prove that coffee or caffeine reduces suicide risk, and it remains possible that individuals with high intake of coffee and caffeine have lower suicide risk for reasons other than caffeine/coffee consumption, such as a lower prevalence of chronic diseases. To minimize this potential bias, we excluded from the analyses individuals with history of cancer or cardiovascular disease at baseline, and conducted

sensitivity analyses adjusted for incidence of these diseases or updating coffee consumption only up to four years before each follow-up interval, thus discounting reductions in coffee consumption that may have been the consequence of incident events predisposing to suicide. The robustness of our findings supports, but does not prove, a protective effect of caffeine.

Caffeine can trigger anxiety and panic attacks in predisposed individuals (Nardi et al. 2007), and thus persons with panic attacks and panic disorder often avoid caffeine. Because anxiety is a risk factor for attempted suicide (and possibly for completed suicide), the lower suicide risk among coffee drinkers may be due to a lower prevalence of anxiety disorders in this group (Pfeiffer et al. 2009; Sareen et al. 2005). To address this possibility, we included in the regression analyses the use of minor tranquilizers, as a proxy for anxiety disorders. The persistence of an inverse association between caffeine and suicide in these analyses is consistent with an effect of caffeine on suicide risk, but residual confounding cannot be excluded. Our inverse associations remained even after adjusting for antidepressant use. However, suicidal person might have been less likely to visit a physician and be treated for depression. Moreover, we lack information on dosage and duration of antidepressant use. Because the participants were predominantly non-Hispanic white health professionals, the generalizability of the observed associations may be limited to similar populations. In particular, individuals with substance dependence problems, which are at high risk of depression and suicide (Martinotti G et al. 2009), are most likely underrepresented in our cohorts. Further, the personality profile of the population included in the study, health professionals, may attenuate some putative effects of caffeine, such as increased impulsiveness and novelty seeking (Gurpegui M et al. 2007; Waldeck and Miller, 1997).

On the other hand, a possible protective effect of caffeine is biologically plausible and deserves serious consideration. Caffeine has complex effects in the central nervous system, largely mediated by antagonism of adenosine A2a and A1 receptors, including an increased turnover of several monoamine transmitters, such as serotonin, dopamine, and noradrenaline (Ferre 2008; Ferre et al. 2008; Fredholm et al. 1999). Therefore, central deficiency of monoamines may be improved by caffeine, which enhances dopaminergic neurotransmission (Ferre 2008; Ferre et al. 2008; Fredholm et al. 1999). 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. These pharmacological effects suggest that caffeine could also act as a mild antidepressant, a hypothesis that could explain the lower risk of depression among coffee drinkers in epidemiological studies (Lucas et al. 2011; Ruusunen et al. 2010).

Caffeine long half-life and possible pharmacokinetic interactions with drugs should also be considered. Peak plasma concentration of caffeine in a cup of coffee is reached within a range of 1 to 1.5h. At dose lower than 10 mg/kg the caffeine half-life range between 2.5 and 4.5h, but it is doubled by use of oral contraceptives or other exogenous estrogens and reduced 30–50% by smoking (Arnaud MJ 1987). Further, because cytochrome P450 1A2 (CYP1A2), which is the primary enzyme in caffeine metabolism, is also important in the metabolism of several medications, including antipsychotics, benzodiazopines, and tricyclic antidepressants (Carrillo and Benitez 2000), changes in caffeine consumption may result in treatment failure or increased risk of toxicity (Patton and Beer 2001). Interactions have been

reported also with lithium, -- caffeine can increase renal lithium clearance and reduce its blood concentrations, thus leading to treatment failure (Patton and Beer 2001). These interactions should be considered when making recommendations on caffeine consumption among individuals using psychoactive drugs.

A protective effect of caffeine on depression and suicide risk would have potentially important clinical and public health implications. Long term moderate caffeine consumption, contrary to early reports, is not associated with an increased risk of cancer, cardiovascular diseases, or total mortality, and overall may have more beneficial than adverse effects (Arab 2010; Lopez-Garcia et al. 2008; Mesas et al. 2011; Winkelmayer et al. 2005). Nonetheless, a general recommendation to increase caffeine consumption may not be justified, because most individuals adjust their caffeine intake to the level that is subjectively optimal for them, and an increase may result in unpleasant side effects (Fredholm et al. 1999). Further, the increased suicide risk associated with heavy coffee consumption in Finland suggests that the response to caffeine could be biphasic; if so, a general recommendation may be difficult, because the optimal dose may depend on caffeine metabolism. This varies substantially between individuals and is affected by genes, cigarette smoking, use of medications, and hormonal factors (Abernethy and Tood 1985; Fredholm et al. 1999; Murphy et al. 1988; Pollock et al. 1999). Lastly, caffeine may even worsen psychiatric symptoms or outcomes in certain sub-groups (Baethge et al. 2009; Nardi et al. 2007). On the other hand, many individuals who are regular caffeine consumers often reduce their caffeine intake unnecessarily because of acute illnesses, surgical procedures, or advice of friends or medical professionals. Some of these reductions could be avoided if it were to be proven that caffeine contributes to prevent depression or suicide. A trial to determine the causality of the association between caffeine and suicide would not be feasible, but a trial of coffee or caffeine and depression severity seems however feasible. Given the association between coffee consumption and smoking, it is important to emphasize that smoking has adverse effects that by far offset any potential benefit of coffee, and quitting smoking remains the most important public health measured for both physical and mental health. Moreover, the common experience of individuals reducing their caffeine intake for a variety of medical or non-medical reasons offers the opportunity to investigate in a clinical trial whether caffeine withdrawal increases the risk of depression or suicidal thoughts.

In summary, our results suggest an association between greater consumption of coffee and a lowered risk of suicide. Further investigations are needed to confirm this finding and to address potential explanatory paths by which usual coffee consumption may contribute to lowered suicide risk.

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Table 1

Baseline Characteristics of Study Participants by Caffeinated Coffee Consumption[a]

	Caffeinated Coffee Consumption (cups[b])								
	Women (NHS, 1992–2008)			Women (NHS II, 1993–2007)			Men (HPFS, 1988–2008)		
	≤1/week (n=17,049)	1/day (n=20,134)	≥4/day (n=6,894)	≤1/week (n=41,459)	1/day (n=11,633)	≥4/day (n=8,121)	≤1/week (n=17,910)	1/day (n=5,646)	≥4/day (n=4,769)
Age (y)	57.5±7.4	58.6±7.1	57.6±6.7	37.6±4.8	38.3±4.6	39.6±4.3	55.3±9.7	56.0±9.7	54.3±8.6
Physical activity (MET-hr/wk)	19.5±23.6	19.4±23.5	18.1±23.2	20.2±26.0	21.8±27.9	21.2±30.0	30.3±34.6	29.9±32.6	27.9±31.9
Body-mass index (kg/m^2)	26.4±5.4	26.1±5.0	25.9±4.8	24.9±5.7	24.3±5.1	24.7±5.0	25.3±3.2	25.5±3.2	25.9±3.1
Past smoker (%)	32.1	43.2	36.5	16.0	26.3	26.4	32.2	41.0	45.6
Current smoker (%)	7.4	11.2	32.8	6.6	9.8	35.4	6.0	8.7	20.0
Married/Partnership (%)	71.1	73.5	57.1	73.3	72.8	65.9	70.3	70.4	68.6
Current menopausal hormones (%)	28.2	29.5	21.7	4.7	4.4	4.6	na	na	na
Minor tranquilizers (%)	2.7	2.3	1.7	1.7	1.7	1.8	1.0	0.8	0.8
Antidepressants (%)	7.1	6.3	5.4	14.4	14.1	16.9	1.0	1.1	1.3
Diet intake[c]									
Caffeine (mg/day)[d]	81±84	234±159	684±174	80±76	199±58	733±113	53±69	190±56	723±113
Decaffeinated coffee (cups/day)	0.5±1.0	0.9±1.2	0.4±1.1	0.3±0.8	0.5±0.8	0.2±0.7	0.7±1.2	0.7±1.2	0.3±0.8
Tea (cups/day)	1.1±1.5	0.6±1.0	0.3±0.8	0.8±1.3	0.6±1.0	0.5±1.0	0.5±0.9	0.5±0.8	0.4±0.9
Alcohol intake (g/day)	3.3±7.8	5.5±9.5	5.8±10.4	1.9±4.6	3.5±5.7	4.5±7.8	8.5±13.6	12.0±14.7	15.0±18.8
≥30 g/day (%)	2.3	3.4	4.6	0.5	0.8	2.3	7.6	11.0	18.0

Abbreviations: HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; MET, metabolic equivalents of task.

[a] Values are reported as mean±SD unless otherwise indicated. Means and percentages are standardized to the age distribution of the study population. Coffee consumption was computed as the cumulative average of intake, but not including changes in intake during the 2-year preceding follow-up periods.

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

[c] Information on diet was obtained in 1990 for the NHS, 1991 for the NHS II, and 1986 for the HPFS.

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

Table 2

Relative Risks (95% CI) of Suicide According to Caffeinated Coffee Consumption[a]

	Caffeinated Coffee Consumption (cups)						
	≤1/week	**2–6/week**	**1/day**	**2–3/day**	**≥4/day**	***P* Value for Trend**	**Increment of 2 cups/day**
NHS							
No. of cases	16	5	14	8	4		
Person-years	257,634	134,745	349,735	294,138	73,749		
RR (95% CI)							
Age-adjusted[b]	1.00	0.63 (0.23, 1.73)	0.69 (0.33, 1.42)	0.40 (0.17, 0.95)	0.67 (0.22, 2.03)	0.19	0.81 (0.54, 1.21)
Age, smoking- adjusted[c]	1.00	0.60 (0.22, 1.66)	0.60 (0.29, 1.25)	0.30 (0.12, 0.71)	0.38 (0.12, 1.20)	0.03	0.66 (0.44, 0.99)
Multivariate[d]	1.00	0.67 (0.24, 1.88)	0.62 (0.29, 1.31)	0.35 (0.14, 0.85)	0.35 (0.11, 1.13)	0.03	0.67 (0.45, 1.01)
Sensitivity[e]	1.00	0.68 (0.24, 1.92)	0.57 (0.26, 1.24)	0.43 (0.19, 0.99)	0.34 (0.10, 1.08)	0.04	0.70 (0.47, 1.04)
NHS II							
No. of cases	24	10	19	9	4		
Person-years	532,352	125,576	244,623	276,714	70,755		
RR (95% CI)							
Age-adjusted[b]	1.00	1.74 (0.83, 3.65)	1.64 (0.89, 3.01)	0.67 (0.31, 1.45)	1.11 (0.38, 3.24)	0.45	0.99 (0.71, 1.39)
Age, smoking- adjusted[c]	1.00	1.68 (0.80, 3.52)	1.43 (0.77, 2.64)	0.49 (0.22, 1.07)	0.53 (0.18, 1.61)	0.03	0.76 (0.54, 1.08)
Multivariate[d]	1.00	1.63 (0.77, 3.42)	1.38 (0.74, 2.57)	0.46 (0.21, 1.01)	0.55 (0.18, 1.65)	0.03	0.74 (0.52, 1.06)
Sensitivity[e]	1.00	1.63 (0.71, 3.72)	1.64 (0.84, 3.18)	0.44 (0.18, 1.07)	0.81 (0.29, 2.26)	0.11	0.86 (0.60, 1.23)
HPFS							
No. of cases	73	22	32	29	8		
Person-years	306,247	105,251	168,482	163,560	51,166		
RR (95% CI)							
Age-adjusted[b]	1.00	0.82 (0.51, 1.34)	0.79 (0.52, 1.21)	0.78 (0.50, 1.21)	0.67 (0.32, 1.40)	0.18	0.88 (0.70, 1.11)
Age, smoking-adjusted[c]	1.00	0.81 (0.49, 1.31)	0.76 (0.50, 1.17)	0.72 (0.46, 1.12)	0.50 (0.24, 1.07)	0.04	0.81 (0.64, 1.02)
Multivariate[d]	1.00	0.81 (0.49, 1.32)	0.74 (0.48, 1.15)	0.65 (0.41, 1.03)	0.49 (0.23, 1.06)	0.02	0.79 (0.62, 1.00)
Sensitivity[e]	1.00	0.89 (0.53, 1.48)	0.77 (0.48, 1.23)	0.86 (0.55, 1.35)	0.44 (0.18, 1.04)	0.09	0.83 (0.65, 1.06)
Pooled results[f]							

	Caffeinated Coffee Consumption (cups)						
	≤1/week	**2–6/week**	**1/day**	**2–3/day**	**≥4/day**	***P* Value for Trend**	**Increment of 2 cups/day**
RR (95% CI)							
Multivariate[d]	1.00	0.97 (0.59, 1.58)	0.86 (0.55, 1.34)	0.55 (0.38, 0.78)	0.47 (0.27, 0.81)	<0.001	0.75 (0.63, 0.90)
With NHS 1982–2008 follow-up[g]	1.00	0.93 (0.65, 1.33)	0.86 (0.64, 1.15)	0.51 (0.37, 0.70)	0.47 (0.30, 0.75)	<0.001	0.74 (0.63, 0.86)

Abbreviations: CI, confidence interval; 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 International Classification of Diseases (ICD).*

[b]Adjusted for age (continuous), time interval and indicator variables for missing data on exposure for each questionnaire.

[c]Further adjusted for smoking status (never smoked, past, currently smoke 1–14, 15–24, or ≥25 cig./day).

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

[e]The same as the multivariate model but using a latency of exposure of 4-year minimum. Number cases were as follow: 47 for NHS, 57 for NHS II, and 149 for HPFS.

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

[g]Results from multivariate models were combined using random-effect model, but the follow-up was 1982 to June 2008 for NHS (cases=108).

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Table 3

Relative Risks (95% CI) of Suicide According to Caffeine Consumption[a]

	Caffeine Consumption (mg/day)						
	≤100	**100–250**	**250–400**	**400–550**	**≥550**	***P* Value for Trend**	**Increment of 300 mg/day**
NHS							
No. of cases	8	19	8	5	7		
Person-years	165,846	322,626	311,137	175,488	134,903		
RR (95% CI)							
Age-adjusted[b]	1.00	1.18 (0.51, 2.71)	0.50 (0.19, 1.34)	0.54 (0.18, 1.66)	0.86 (0.31, 2.39)	0.28	0.81 (0.52, 1.27)
Age, smoking-adjusted[c]	1.00	1.06 (0.46, 2.46)	0.41 (0.15, 1.10)	0.40 (0.13, 1.24)	0.51 (0.17, 1.47)	0.05	0.64 (0.41, 1.02)
Multivariate[d]	1.00	0.99 (0.42, 2.31)	0.42 (0.15, 1.15)	0.46 (0.15, 1.45)	0.49 (0.17, 1.42)	0.06	0.66 (0.42, 1.04)
Sensitivity[e]	1.00	1.00 (0.43, 2.36)	0.32 (0.11, 0.93)	0.64 (0.22, 1.81)	0.46 (0.16, 1.34)	0.05	0.70 (0.45, 1.08)
NHS II							
No. of cases	13	28	14	6	5		
Person-years	390,687	373,038	270,719	117,755	97,821		
RR (95% CI)							
Age-adjusted[b]	1.00	2.19 (1.13, 4.23)	1.45 (0.68, 3.09)	1.42 (0.54, 3.75)	1.39 (0.49, 3.92)	0.85	1.05 (0.74, 1.51)
Age, smoking-adjusted[c]	1.00	1.92 (0.99, 3.73)	1.12 (0.52, 2.43)	0.94 (0.35, 2.53)	0.67 (0.23, 1.99)	0.16	0.77 (0.52, 1.12)
Multivariate[d]	1.00	1.85 (0.95, 3.59)	1.05 (0.48, 2.27)	0.86 (0.32, 2.31)	0.61 (0.21, 1.80)	0.10	0.73 (0.50, 1.07)
Sensitivity[e]	1.00	1.71 (0.82, 3.57)	1.23 (0.54, 2.80)	1.08 (0.39, 3.00)	0.91 (0.32, 2.60)	0.52	0.87 (0.59, 1.28)
HPFS							
No. of cases	62	49	35	6	12		
Person-years	291,418	210,844	159,937	67,308	65,200		
RR (95% CI)							
Age-adjusted[b]	1.00	1.10 (0.75, 1.61)	1.06 (0.70, 1.62)	0.47 (0.20, 1.10)	0.93 (0.49, 1.74)	0.48	0.91 (0.72, 1.16)
Age, smoking- adjusted[c]	1.00	1.10 (0.75, 1.61)	1.02 (0.67, 1.56)	0.45 (0.19, 1.05)	0.74 (0.39, 1.40)	0.18	0.84 (0.66, 1.07)
Multivariate[d]	1.00	1.06 (0.72, 1.56)	0.95 (0.62, 1.47)	0.41 (0.17, 0.97)	0.71 (0.37, 1.37)	0.12	0.82 (0.64, 1.05)
Sensitivity[e]	1.00	0.99 (0.66, 1.49)	1.13 (0.73, 1.76)	0.46 (0.20, 1.10)	0.60 (0.29, 1.25)	0.17	0.86 (0.67, 1.12)
Pooled results[f]							

	Caffeine Consumption (mg/day)						
	≤100	**100–250**	**250–400**	**400–550**	**≥550**	***P* Value for Trend**	**Increment of 300 mg/day**
RR (95% CI)							
Multivariate[d]	1.00	1.20 (0.85, 1.69)	0.86 (0.57, 1.30)	0.54 (0.30, 0.94)	0.63 (0.39, 1.04)	0.005	0.77 (0.63, 0.93)
With NHS 1982–2008 follow-up[g]	1.00	1.07 (0.81, 1.42)	0.79 (0.58, 1.09)	0.45 (0.28, 0.73)	0.55 (0.36, 0.84)	<0.001	0.74 (0.63, 0.88)

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

[a]Caffeine was calculated from coffee and non-coffee sources (tea, caffeinated soft drink, chocolate). Cases of suicide were codes E950 to E959 according the *Eight Revision International Classification of Diseases (ICD).*

[b]Adjusted for age (continuous), time interval and indicator variables for missing data on exposure for each questionnaire.

[c]Further adjusted for smoking status (never smoked, past, currently smoke 1–14, 15–24, or ≥25 cig./day).

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

[e]The same as the multivariate model but using a latency of exposure of 4-year minimum. Number cases were as follow: 47 for NHS, 57 for NHS II, and 149 for HPFS.

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

[g]Results from multivariate models were combined using random-effect model, but follow-up was 1982 to June 2008 for NHS (cases=108).

Table 4

Relative Risks (95% CI) of Suicide According to Decaffeinated Coffee Consumption[a]

	Decaffeinated Coffee Consumption (cups)					
	≤1/week	**2–6/week**	**1/day**	**≥2/day**	***P* Value for Trend**	**Increment of 1 cup/day**
NHS						
No. of cases	26	8	11	2		
Person-years	468,072	369,499	202,131	70,299		
RR (95% CI)						
Age-adjusted[b]	1.00	0.52 (0.23, 1.18)	1.24 (0.59, 2.61)	0.52 (0.12, 2.21)	0.96	1.06 (0.78, 1.44)
Age, smoking-adjusted[c]	1.00	0.57 (0.25, 1.31)	1.25 (0.59, 2.68)	0.47 (0.11, 1.99)	0.82	1.01 (0.74, 1.37)
Multivariate[d]	1.00	0.55 (0.23, 1.30)	1.29 (0.59, 2.79)	0.54 (0.12, 2.33)	0.99	1.04 (0.76, 1.43)
Sensitivity[e]	1.00	0.56 (0.24, 1.31)	1.07 (0.47, 2.45)	0.70 (0.21, 2.40)	0.91	1.02 (0.74, 1.39)
NHS II						
No. of cases	41	20	2	3		
Person-years	777,390	323,200	101,075	48,355		
RR (95% CI)						
Age-adjusted[b]	1.00	1.13 (0.66, 1.94)	0.35 (0.08, 1.43)	1.05 (0.32, 3.43)	0.53	0.93 (0.63, 1.35)
Age, smoking-adjusted[c]	1.00	1.28 (0.74, 2.19)	0.36 (0.09, 1.50)	0.96 (0.29, 3.14)	0.47	0.91 (0.63, 1.31)
Multivariate[d]	1.00	1.29 (0.75, 2.23)	0.37 (0.09, 1.55)	0.97 (0.29, 3.19)	0.49	0.91 (0.63, 1.31)
Sensitivity[e]	1.00	1.10 (0.60, 2.03)	0.42 (0.10, 1.74)	1.08 (0.33, 3.58)	0.69	1.03 (0.73, 1.45)
HPFS						
No. of cases	89	41	24	10		
Person-years	361,414	257,832	106,582	68,878		
RR (95% CI)						
Age-adjusted[b]	1.00	0.62 (0.42, 0.90)	0.90 (0.57, 1.43)	0.55 (0.29, 1.08)	0.23	0.87 (0.72, 1.05)
Age, smoking- adjusted[c]	1.00	0.61 (0.42, 0.90)	0.90 (0.56, 1.44)	0.53 (0.27, 1.03)	0.19	0.86 (0.71, 1.04)
Multivariate[d]	1.00	0.64 (0.43, 0.94)	0.95 (0.59, 1.54)	0.57 (0.29, 1.12)	0.28	0.89 (0.73, 1.07)
Sensitivity[e]	1.00	0.66 (0.44, 0.99)	1.03 (0.63, 1.68)	0.56 (0.28, 1.11)	0.29	0.88 (0.73, 1.06)
Pooled results[f]						

	Decaffeinated Coffee Consumption (cups)					
	≤1/week	**2–6/week**	**1/day**	**≥2/day**	***P* Value for Trend**	**Increment of 1 cup/day**
RR (95% CI)						
Multivariate[d]	1.00	0.79 (0.47, 1.32)	0.95 (0.61, 1.48)	0.63 (0.37, 1.09)	0.26	0.92 (0.80, 1.07)

Abbreviations: CI, confidence interval; 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 International Classification of Diseases (ICD).*

[b]Adjusted for age (continuous), time interval and indicator variables for missing data on exposure for each questionnaire.

[c]Further adjusted for smoking status (never smoked, past, currently smoke 1–14, 15–24, or ≥25 cig./day).

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

[e]The same as the multivariate model but using a latency of exposure of 4-year minimum. Number cases were as follow: 47 for NHS, 66 for NHS II, and 164 for HPFS.

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