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Reproductive factors, exogenous estrogen use and risk of Parkinson's disease

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Abstract

To determine if reproductive factors or exogenous estrogen are associated with risk of Parkinson's disease (PD), we conducted a prospective study with 22 years of follow-up among post-menopausal participants in the Nurses' Health Study. Relative risks (RRs) and 95% confidence intervals (CIs) of PD were estimated from a Cox proportional hazards model adjusting for potential confounders. Risk of PD was not significantly associated with any of the reproductive factors measured or exogenous estrogen use. Use of post-menopausal hormones, however, may modify the associations of smoking and caffeine intake with PD risk. The inverse relation between smoking and PD risk was attenuated among ever users of post-menopausal hormones (p for interaction = 0.05). Similar results were obtained for caffeine (p for interaction = 0.09). In exploratory analyses, women using progestin-only hormones were found to have an increased PD risk, but this result was based on a very small number of cases ($n=4$). In this large longitudinal study, we found no evidence of a beneficial effect of exogenous or endogenous estrogens on risk of PD. The use of post-menopausal hormone use may interact with other risk factors, but findings are preliminary and need confirmation in other populations.

Introduction

An increased risk of Parkinson's disease (PD) in men compared to women is well established; men are approximately two times as likely as women to develop the disease^{1, 2}. Experimental evidence supports a potential neuroprotective role for estrogens. Specifically, ovariectomized and male animals have decreased dopaminergic functioning compared to females with intact ovaries,³ and nigrostriatal dopaminergic damage following administration of neurotoxic agents

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is reduced in females compared to males^{4, 5}. Additionally, administration of β -estradiol *in vitro* and in animal models of PD attenuates injury or reduces depletion of dopamine induced by neurotoxic agents⁶.

The association between estrogen use and risk of PD may be modified by other factors, specifically caffeine and smoking. Results of epidemiological studies suggest a reduced risk of PD associated with caffeine intake⁷ among women who do not use post-menopausal hormones (PMHs), but not among PMH users^{8, 9}. This epidemiologic observation has been further supported by experimental evidence in ovariectomized mice in which caffeine confers neuroprotection with lower potency when estrogen (rather than placebo) is administered¹⁰. Similarly, there is consistently strong evidence that smoking is associated with a decreased risk of PD⁷ and exposure to smoking may increase circulating levels of estrogens¹¹.

Epidemiologic evidence assessing the association between reproductive factors and hormone use and risk of PD has been inconsistent. In particular, use of PMHs has been associated with decreased risk in two studies^{12, 13}, while no association has been found in others^{9, 14–17}. Further, the effect of PMHs is possibly dependent on type of menopause¹⁷. Some of these inconsistencies may be due to the retrospective exposure assessment and lack of consideration of smoking and other potential confounders in many of these studies.

To explore the potential role of endogenous and exogenous estrogen exposure and risk of PD, we conducted a prospective cohort study amongst participants in a large, longitudinal cohort, the Nurses' Health Study (NHS). This prospective exposure assessment allows for detailed information on reproductive history and importantly, PMH use, which may vary over time. Because post-menopausal hormones may be a combination of progestin and estrogens, we have also utilized detailed information on preparation type to further explore this relationship. Progesterone has been shown to be neuroprotective and potentially modulate the activity of estrogen in PD animal models^{18, 19}. Therefore, the specific type of hormone used may be relevant to assess the relationship with risk of PD.

Methods

Study population

The study population included participants in the Nurses' Health Study. Briefly, the NHS cohort began in 1976 when 121,701 nurses aged 30–55 from one of eleven states returned mailed questionnaires regarding lifestyle factors, medical conditions and disease history²⁰. The follow-up period lasted from the return date of the 1980 questionnaire or the date of the questionnaire in which a woman reported her periods had permanently ceased to the date of diagnosis of PD, death, date of diagnosis of stroke, loss to follow-up or the end of the study (June 30, 2002). Women with prevalent and incident stroke as well as prevalent PD were excluded from the analysis.

PD ascertainment

Case ascertainment for PD has been previously described²¹. Briefly, a question on lifetime occurrence of PD was first asked in 1994 and updated biennially. Participants who reported PD were asked permission to obtain from the treating neurologist (or internist or general practitioner) either a questionnaire confirming the diagnosis of PD or a copy of the medical records. A case is confirmed if the diagnosis is considered clinically definite or probable by the treating neurologist or internist, or if the medical record includes either a final diagnosis of PD made by a neurologist, or evidence at a neurological examination of at least 2 of the 3 cardinal signs (rest tremor, rigidity, and bradykinesia) in the absence of clinical features suggesting other diagnoses²² or non-responsiveness to levodopa treatment. The review of

medical records was conducted by the investigators, blind to the exposure status. Overall, the diagnosis was confirmed by the treating neurologist in 87.4 % of the cases, by review of the medical records in 4.7 %, and by the treating internist without further support in the remaining 7.9 %.

In addition to self-reported PD, cases were also ascertained through examination of death certificates. Deaths are reported through next of kin, coworkers, postal authorities or the National Death Index and the follow-up for deaths in this cohort has been estimated to be 98%²³. If PD was reported on the death certificate, permission was requested from the family to confirm disease in the same manner as previously described.

Exposure assessment

Menopause, menarche and parity—In 1976, women were asked their age of menarche and menopausal status. Further questions were asked of menopausal women, including age at menopause and type of menopause - natural, surgical, or radiation. Menopausal status was updated biennially. Parity, defined as pregnancy lasting at least 6 months, was assessed at baseline and biennially through 1984 and again in 1996. For variables that may change over time, these were assessed through the biennial questionnaires and exposure status updated. The accuracy of self-reported age at menopause, age at menarche and type of menopause has been validated in this cohort²⁴.

Post-menopausal hormone use (PMHs)—A question on PMH use was asked biennially beginning in 1976. Specifically, at baseline, women were asked if following the cessation of menstruation, did they take female hormones and if so, for how long. Beginning in 1984, women were asked about specific types of PMH use allowing classification of estrogen only, progestin only or combination hormone use.

Oral contraceptive use—Oral contraceptive use was asked at baseline and biennially until 1984, at which point no women reported current use and therefore, after 1984, use was defined as ever/never. The validity of self-reported information regarding oral contraceptives has been validated in a complementary cohort, the Nurses' Health Study II²⁵.

Assessment of covariates

The 1980 survey included a food frequency questionnaire (FFQ) for the first time to assess participants' dietary habits during the past year. Dietary surveys were updated roughly every four years thereafter. The reproducibility and validity of these FFQs have been assessed by comparison with detailed dietary records²⁶.

Smoking history was first reported on the 1976 questionnaire and then updated biennially. Questions at baseline for current smokers included number of daily cigarettes and questions at baseline for ever smokers included average number of daily cigarettes. On subsequent questionnaires, current smoking information was updated biennially and updated pack-years of smoking thus calculated. Adult height was asked in 1976 and body weight was updated biennially; body mass index (BMI) was calculated by dividing height in kilograms by the square of height in meters. Total physical activity was calculated in metabolic equivalent tasks (METs)²⁷.

Data Analysis

Cox proportional hazards models were used to calculate relative risks (RRs) and 95% confidence intervals (CIs) to assess the association between parity, PMH use, OC use, age at menopause and age at menarche and risk of PD adjusting for age in years and pack-years of smoking; multivariate analyses further controlled for alcohol consumption (average g/day),

caffeine intake (average cumulative mg/day), physical activity (METS/wk) and BMI (kg/m²: <23, 23–25, 25–27, 28–30, 30+).

These multivariate analyses generated results similar to the age- and smoking-adjusted estimates and therefore the age- and smoking-adjusted estimates are presented. Further, sensitivity analyses were conducted including only cases with a clinical definite diagnosis of PD or with diagnoses by a neurologist or movement disorder specialist and did not materially change results. Potential interactions between PMH use and caffeine intake or cigarette smoking were examined by including a multiplicative interaction term in the smoking- and age-adjusted model and the statistical significance was evaluated using a likelihood ratio test. The interaction term was defined as a cross-product of either caffeine consumption (mg/day) or pack-years of smoking and use of PMH (ever vs. never).

Results

A total of 244 incident cases were identified during the follow-up period with an average age of diagnosis of 65.7 years. Baseline population characteristics according to type of menopause, use of PMHs and use of OCs upon entry are shown in Table 1.

Risk of PD, adjusted for age and smoking history, was not associated with PMH use, parity, age at menopause, OC use, number of reproductive years (years between menarche and menopause) or type of menopause (Table 2). Further, no increased PD risk was observed among women who underwent bilateral oophorectomy at a young age compared to women with natural menopause (RR=0.8, 95% CI=0.4, 1.4, for oophorectomy <38years), though this result was based on a small number of cases (n=12). There seemed to be a non-significant trend towards lower risk for older age at menopause amongst women with natural menopause. Every five years delay in age at menopause was associated with an 11% reduction in the risk of PD (RR=0.89 95% CI=0.72, 1.09, p for trend=0.27). There was also a significant positive association with OC use. Each additional five years of OC use was associated with a 20% increased risk of PD (RR=1.20, 95% CI=1.00, 1.43, p for trend=0.048).

PMH use was, in general, not associated with PD risk (Table 2), although progestin alone use was associated with a 3-fold higher PD risk (RR=3.41, 95% CI= 1.23, 9.47; p=0.02). However, this finding should be interpreted cautiously as the analyses were based on a small number of cases. In subgroup analyses, estrogen only use tended to be associated with a higher PD risk among women with natural menopause (RR=1.67, 95% CI=1.08, 2.57; p=0.02). However, use of estrogen only or with progestin was not associated with PD risk in analyses amongst all post-menopausal women or amongst women with surgical menopause.

No statistically significant interaction between caffeine and post-menopausal hormone use as observed (Table 3). However, as in our previous studies, the inverse association between caffeine intake and PD risk seemed to be limited to never users of PMHs (p for trend=0.05), while no association was observed amongst ever users. Results were similar in analysis using baseline exposure information or when cases diagnosed in the first 4 years of follow-up were excluded. Likewise, current PMH use compared to never use tended to be related to a lower PD risk among individuals with low caffeine consumption (<100mg/day) (RR=0.68, 95% CI=0.31, 1.50), and to a higher risk amongst those with higher intakes (>100mg/day) (RR=1.29, 95% CI=0.93, 1.80), but neither trend was statistically significant.

We observed a significant interaction between smoking and PMH use on PD risk (p=0.05, Table 3). Although the inverse relationship between pack-years of smoking and PD risk was observed in both ever and never users of PMH, the association appeared stronger among never users (Table 3). For each ten pack-year increase in smoking, the risk of PD was reduced by 28% amongst never users of PMHs (RR=0.72, 95% CI=0.61, 0.85, p=0.0001) and only 13%

amongst ever users (RR=0.87, 95% CI=0.79, 0.96, p=0.005). These results remained significant in analysis using baseline exposure information or in the four year lag analysis. When considering the combined risk of smoking and PMH use, smoking in the highest three quintiles conferred more protection amongst never users of PMHs than ever users (Figure). Similarly, the association between PMH use and risk of PD varied by smoking status. Amongst ever smokers, current PMH use was related to a significantly increased risk of PD compared to never users (RR=1.75, 95% CI=1.11, 2.77; p=0.02), but not amongst never smokers.

Discussion

In this large longitudinal investigation, overall, we did not find any association between reproductive factors or use of exogenous estrogens and risk of PD.

Strengths of this study include the prospective design, the high follow-up rates, and use of repeated and validated assessment of reproductive factors and hormone use. In a sub-set of this cohort the mean levels of estradiol amongst postmenopausal women reporting current use of PMH were found to be well in excess of that for women not using PMHs²⁸. Further, the validity of history of estrogen use and reproductive factors in our study is supported by the previous finding that these factors were strong predictors of ovarian and breast cancer in this cohort^{29, 30}. Although the confirmation of PD diagnoses relied on reports from the treating neurologists or review of the medical records rather than on direct physical examination of all participants, and some diagnostic errors are inevitable, recent clinicopathological studies have shown that the diagnosis of PD made by neurologists or movement disorder specialists has a high positive predictive value^{31, 32}, and bias from this source is thus likely to be modest. Notably, results were not affected when analyses were restricted to cases diagnosed by a neurologist.

Also, we cannot exclude the possibility that an effect of hormones on PD disease would become manifest only at a very late age, although the fact that we found similar results for PD with onset before or after 65 years of age provides some evidence against this possibility. Additionally, although the timing of initiation of PMH use could be important for some disease outcomes^{33, 34}, we were unable to address this question in relation with PD because the majority of women (80%) began using hormones around the time of menopause³⁵, and therefore numbers were too small to explore a possible effect of late initiation of hormone use.

Finally, because reproductive factors and use of hormones correlate with other aspects of lifestyle, confounding is an important concern, and the availability of prospectively collected and validated information on strong risk factors, such as smoking and caffeine, is an important feature of our study. Nevertheless, as in all observational studies, residual confounding from unmeasured factors cannot be excluded.

Our findings are consistent with previous epidemiologic studies showing no association between PMH use and risk of PD^{14–17}, but not with those showing a decreased risk associated with PMH use^{12, 13}. Further, we could not confirm the observation of increased risk of PD associated with estrogen only or combination PMH use amongst women with hysterectomy reported in a recent nested case-control study¹⁷. We also did not confirm the recent finding of a possibly increased risk of parkinsonism associated with oophorectomy³⁶. The number of women with oophorectomy in our study, however, was too small to exclude a moderate association. Even in the previous investigation, which was based on the follow-up of more than 2000 women with pre-menopausal oophorectomy, a significant increase in risk among oophorectomized women was found only in analyses including all cases of parkinsonism. Prior studies did not explore different types of PMHs, as in the current investigation. In sub-analyses exploring the relationship between types of post-menopausal hormones and risk of PD, a three-fold increased risk was observed with use of progestin-only hormones. However, this is based

on a small number of cases and requires confirmation. Experimental evidence regarding the potential role of progestins in neuroprotection is inconsistent and although progesterone administration has been shown to be neuroprotective, common synthetic progestins found in post-menopausal hormones may not exert the same neuroprotective effect^{18, 37}.

Our finding of no association between age at menopause and risk of PD is consistent with some studies^{15, 16}, but not another in which older age at menopause was associated with decreased risk of PD¹⁷. We did not find an association between parity and risk of PD consistent with a recent investigation¹⁷, in contrast with a case-control study showing increased risk of PD associated with increased duration of pregnancies¹⁶. The authors hypothesized that this could be explained by differences in estrogen metabolism and serum hormone binding protein (SHBG) amongst nulliparous compared to parous women. However, several studies of serum hormones have shown no differences related to parity associated with serum levels of estrogens^{38, 39} or SHBG amongst pre- and post-menopausal women^{38, 40}. Lastly, we did not confirm the previously reported increased risk of PD associated with decreased years between menarche and menopause¹⁶.

We have previously reported significant interactions between caffeine intake and PMH use on risk of PD, in which the inverse relationship between caffeine and PD risk was only amongst never users of PMHs, while not amongst ever users. This interaction was still suggested in the current analysis, albeit appeared to be weaker than in our previous reports^{8, 9}. This attenuation is consistent with the fact that most women in this cohort have ceased use of PMHs in recent years, and any effect of PMH use is likely diminishing over time. Supportively, this interaction was also suggested in animal experiments in which the neuroprotective effect of caffeine is reduced when estrogen is administered¹⁰.

The potential interaction with smoking is consistent with previous findings in this cohort⁹. Attenuation of the association between smoking and PD in the presence of estrogen suggests an interaction in which estrogen or its metabolites may block the activity of a protective pathway. Nicotine metabolism is increased in females compared to males and in the presence of administration or use of exogenous estrogens⁴¹. Thus, an increase in nicotine metabolism could result in decreased availability of a substrate important in a potential neuroprotective pathway. The mechanism by which estrogen could antagonize a putative protective effect of nicotine is, however, unclear.

The mechanism by which estrogen confers neuroprotection is unclear and likely complex. Several pathways have been suggested⁶, including anti-inflammatory properties⁴², anti-oxidant effects⁴³, and regulating apoptotic pathways. The results of our study could be explained if either the reproductive factors investigated or use of post-menopausal hormones have at most modest effects on PD risk, or if their effects are modified by other behavioral, environmental, or genetic factors that remain to be identified. The suggestion in our data of interactions between post-menopausal hormones and smoking or caffeine is consistent with this possibility that seems worthy of further investigation in epidemiological and experimental studies.

In summary, the results of this large longitudinal study do not support a beneficial role for endogenous estrogen or use of post-menopausal hormones on risk of PD. Although risk of PD was higher among women using progestin only PMHs, this was a marginal finding based on small numbers.

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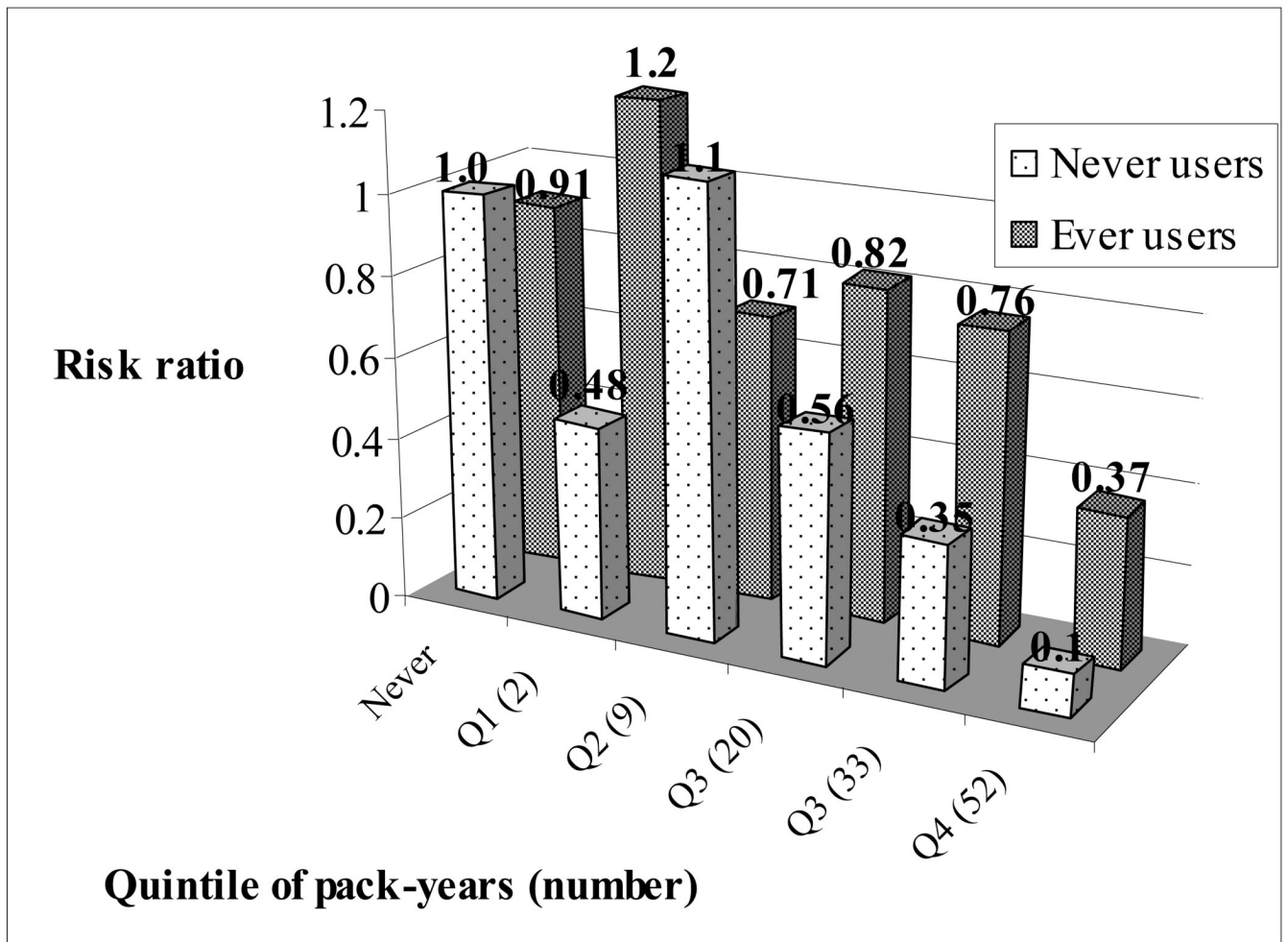


Figure. Combined effect of PMHs and smoking (pack-years) on risk of PD adjusted for age
Referent is never smokers who never used PMHs

Table 1
 Baseline characteristics according to post-menopausal hormone use, oral contraceptive use and type of menopause

	<i>PMH use</i>			<i>OC use</i>			<i>Menopause type</i>	
	Never	Past	Current	Never	Ever	Natural	Surgical	
Age (yrs)	51.0	52.7	50.8	52.3	49.3	52.8	48.6	
Current smoker (%)	31.0	31.1	25.5	28.3	30.3	31.7	26.8	
Past smoker (%)	37.3	40.4	40.0	37.5	41.1	40.2	38.1	
BMI (kg/m ²)	25.1	24.7	23.7	24.8	24.1	24.2	24.6	
Caffeine (mg/day)	400.3	390.5	387.5	392.5	394.9	400.7	383.1	
Alcohol (g/day)	6.2	6.6	6.7	6.1	7.1	6.6	6.2	
Age at menopause (yrs)	47.6	45.3	47.0	47.5	47.0	49.9	43.9	

Other than age, all estimates are standardized to the age distribution of the cohort.

Table 2
Relative risk of PD associated with reproductive factors

	Person-years	No. Cases	RR (95% CI)	p - value
PMH use				
Never	556088	88	REF	NA
Past	292596	63	1.08 (0.78, 1.50)	
Current	474192	89	1.18 (0.88, 1.59)	
<hr/>				
Duration of PMH use				
Never	556088	88	REF	0.79
<5	386748	68	1.14 (0.83, 1.57)	
>=5	380039	84	1.14 (0.84, 1.54)	
<hr/>				
Time since last PMH use				
Never	556088	88	REF	0.23
>24 months	118059	33	1.26 (0.86, 1.89)	
<=24 months	30111	6	1.15 (0.50, 2.64)	
Current	407848	80	1.19 (0.87, 1.63)	
<hr/>				
Type of PMH use				
Non-users	432062	78	REF	NA
Estrogen only	258876	67	1.28 (0.93, 1.78)	
Progesterone only	12782	4	3.41 (1.23, 9.47)	
Combination	213966	36	0.97 (0.65, 1.44)	
Unknown	208500	40	1.04 (0.71, 1.54)	
<hr/>				
Age at menopause[†]				
< 45	85523	17	REF	0.27
45–49	206904	42	0.89 (0.51, 1.57)	
50–54	374365	82	0.74 (0.44, 1.25)	
>=55	48397	11	0.60 (0.28, 1.28)	
<hr/>				
Menopause type				
Natural	729624	152	REF	NA
Surgical, 0–1 ovaries	220809	42	0.79 (0.69, 1.36)	
Surgical, 2 ovaries	267442	34	0.97 (0.44, 1.44)	
<hr/>				
OC use				
Never	766291	164	REF	0.89
Ever	556586	76	1.02 (0.77, 1.36)	
<hr/>				
Duration of OC use				
Never	766291	164	REF	0.05
< 5	371509	40	0.84 (0.59, 1.19)	

	Person-years	No. Cases	RR (95% CI)	p - value
>= 5	185040	36	1.35 (0.93, 1.96)	
Number of children				
<2	169608	26	REF	>0.99
2-3	698052	119	1.20 (0.78, 1.83)	
>3	422515	89	1.22(0. 78, 1.89)	
Age at menarche				
<12	293589	48	REF	0.67
12	347224	63	1.06 (0.73, 1.55)	
13	402642	71	1.02 (0.70, 1.46)	
>13	268513	55	1.07 (0.73, 1.58)	

Adjusted for smoking in pack-years.

[‡] amongst women with natural menopause

Table 3

Relative risk of PD associated with smoking history and caffeine intake according to PMH use

	Hormone Use	
	Never (n=88)	Ever (n= 152)
Smoking history (median pack-years)		
Never	1.0 (Ref)	1.0 (Ref)
Q1 (2)	0.48 (0.19, 1.21)	1.31 (0.81, 2.11)
Q2 (9)	1.14 (0.61, 2.13)	0.78 (0.44, 1.39)
Q3 (20)	0.57 (0.26, 1.26)	0.85 (0.49, 1.47)
Q4 (33)	0.37 (0.15, .92)	0.79 (0.44, 1.39)
Q5 (52)	0.11 (0.03, 0.43)	0.36 (0.17, 0.75)
p for trend	0.0001	0.005
Caffeine intake (median mg/day)		
Q1 (68)	1.0 (Ref)	1.0 (Ref)
Q2 (179)	0.80 (0.44, 1.46)	1.33 (0.84, 2.13)
Q3 (306)	0.84 (0.46, 1.52)	0.90 (0.54, 1.49)
Q4 (414)	0.58 (0.29, 1.16)	0.57 (0.31, 1.04)
Q5 (665)	0.54 (0.25, 1.14)	1.13 (0.66, 1.93)
p for trend	0.05	0.60

Adjusted for age and smoking history (for caffeine analysis).