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Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease

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Abstract

Objective—To determine whether history of hypertension, hypercholesterolemia, or diabetes is associated with risk of Parkinson disease (PD).

Methods—Prospective study among participants in two large cohorts: the Nurses' Health Study (121,046 women) and the Health Professionals Follow-up Study (50,833 men). Mean duration of follow-up was 22.9 years in women, aged 30 to 55 years at baseline, and 12.6 years in men, aged 40 to 75 years at baseline. Relative risks (RRs) of PD were estimated from a Cox proportional hazards model adjusting for potential confounders.

Results—We identified a total of 530 incident cases of PD during the follow-up. Risk of PD was not associated with self-reported history of hypertension (RR = 0.96, 95% CI = 0.80 to 1.15), high cholesterol (RR = 0.98, 95% CI = 0.82 to 1.19), or diabetes (RR = 1.04, 95% CI = 0.74 to 1.46), after adjusting for age and smoking in pack-years. Risk of PD decreased modestly with increasing levels of self-reported total cholesterol (RR for a 50-mg/dL increase in total cholesterol = 0.86, 95% CI = 0.78 to 0.95, *p* for trend = 0.02), but use of cholesterol-lowering drugs was not associated with PD risk (RR comparing users with nonusers = 0.85, 95% CI = 0.59 to 1.23). Among individuals with PD, systolic blood pressure was similar to noncases up to the time of diagnosis but declined afterward.

Conclusions—Results of this large prospective study suggest that Parkinson disease risk is not significantly related to history of hypertension, hypercholesterolemia, or diabetes but may modestly decline with increasing blood cholesterol levels.

Hypertension, hypercholesterolemia, and diabetes are important risk factors for atherosclerosis¹ and have been associated with an increased incidence of stroke,² Alzheimer disease,³ and dementia.⁴ Although the etiology of Parkinson disease (PD) is poorly understood, vascular factors may be influential in modulating disease risk.

Epidemiologic studies of vascular conditions as risk factors for PD have been sparse and generally limited to a few case-control studies in which the temporal relationship between exposure and disease onset was often unclear. Results from these studies have been inconsistent regarding the risk of PD associated with a history of hypertension or diabetes.^{5–9} In a more recent case-control study, in which medical history was verified through medical record

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review, a decreased risk of PD was associated with a history of diabetes, and this effect was stronger in men and particularly in male nonsmokers.¹⁰

To address the hypothesis that a history of vascular conditions may contribute to the risk of PD, we analyzed these associations in two large prospective cohorts. A prospective design is important in assessing these associations, because changes in blood pressure or cholesterolemia could occur early in PD, and possibly before the onset of neurologic symptoms, as a result of changes in autonomic function, diet, or physical activity. In addition to considering vascular disease history, we examined changes in blood pressure over time relative to diagnosis using self-reported values for systolic (SBP) and diastolic blood pressure (DBP).

METHODS

Study population

The study population includes participants in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS). The NHS cohort began in 1976 when 121,700 registered nurses in 11 states aged 30 to 55 years returned mailed questionnaires including information on disease history and lifestyle factors.¹¹ The HPFS cohort was established in 1986 when 51,529 male health professionals (dentists, optometrists, veterinarians, osteopaths, podiatrists, and pharmacists) aged 40 to 75 years returned a mailed questionnaire with similar information. Questionnaires were mailed biennially to both cohorts to update information on newly diagnosed disease and potential risk factors.

Exclusion criteria included prevalent stroke and prevalent PD. In total, 50,833 men and 121,046 women were followed to the date of PD, date of death, date of stroke, or the end of the follow-up period (January 31, 2000 for HPFS and June 31, 2000 for NHS).

Case ascertainment

A specific question on lifetime occurrence of PD was first asked in 1988 for men and 1994 for women, and then updated every 2 years. Ascertainment of PD in these cohorts has been previously described.¹² Briefly, after obtaining permission from participants who reported a new diagnosis of PD, we asked the treating neurologist (or internist if the neurologist did not respond) to complete a questionnaire to confirm the PD diagnosis and report the certainty of the diagnosis, or to send a copy of the medical record. A case was confirmed if the diagnosis was considered definite or probable by the treating neurologist or internist, or if the medical record included either a final diagnosis of PD made by a neurologist, or if there was evidence at a neurologic examination of at least two of the three cardinal signs (rest tremor, rigidity, or bradykinesia) in the absence of features suggesting other diagnoses. The review of medical records was conducted by a movement disorder specialist, blinded to the exposure status. Overall, the diagnosis was confirmed by the treating neurologist in 82.3% of the cases, by the treating internist in 14.6%, and by review of the medical records in 3.1%.

Hypertension, high cholesterol, and diabetes

History of physician-diagnosed hypertension, high cholesterol, and diabetes was assessed at baseline (1976 for women and 1986 for men) and updated every 2 years thereafter. The main analyses were based on self-reported history of these conditions. Additionally, we also considered a more inclusive definition of hypertension—a self-report of doctor-diagnosed hypertension, SBP >160 mmHg, DBP > 90 mmHg, or reported use of antihypertensive medication. Likewise, history of hypercholesterolemia was additionally defined as self-reported doctor-diagnosed high cholesterol or use of cholesterol-lowering medication. History of diabetes was defined as ever reporting of doctor-diagnosed diabetes. Once a participant reported any of the previous conditions, he or she was considered to have a positive history of

hypertension, hypercholesterolemia, or diabetes, as appropriate, until the end of the follow-up. The accuracy of self-reported cardiovascular risk factors and disease has been validated among participants in the NHS.¹³ Further, in the HPFS cohort, the association between coronary heart disease mortality and diabetes has been shown to be similar whether self-reported (relative risk [RR] = 3.84) or confirmed diagnoses were used to determine disease history (RR = 3.67).¹⁴

Medication use

History of antihypertensive, cholesterol-lowering, and diabetic medication use was assessed on the biennial questionnaires. Among women, individual drugs included in the follow-up questionnaires included thiazide diuretics (1980, 1982, 1988, 1994, 1996, 1998); calcium-channel blockers, beta-blockers, other anti-hypertensives, cholesterol-lowering drugs (1988, 1994, 1996, 1998); and angiotensin-converting enzyme (ACE) inhibitors (1996 and 1998). In men, use of thiazide diuretics, calcium-channel blockers, beta-blockers, other antihypertensives, and cholesterol-lowering drugs was assessed every 2 years, all starting in 1986, except for thiazide diuretics that were added in 1992; information on ACE inhibitors was not collected until after 1998 and were therefore not included in the present analysis.

For analyses considering ever use of antihypertensive or cholesterol-lowering medications, we used 1988 as the baseline in women, because this was the first year that the majority of medications were reported. Participants who reported medication use were considered to have a positive history of medication use throughout follow-up.

Systolic blood pressure, diastolic blood pressure, and total serum cholesterol

To examine the temporal changes of blood pressures among PD patients before and after the diagnosis, we used information on typical resting blood pressure that was collected first in 1988, and then in 1990, 1992, and 1996 in the HPFS cohort and in 1988, 1990, 1994, and 1998 in the NHS cohort. Participants reported blood pressure according to predefined ranges and, for purpose of the present analyses, individual levels of blood pressure were assigned the midpoints of those ranges. Analyses include information from all years in which blood pressures were reported, except for 1988 in men, because the format of the coding changed from 1988 to 1990 and did not allow for consistent exposure assignment. In primary analyses, individuals who reported antihypertensive medication (as described above) use were assigned to the highest category of blood pressure (SBP > 160 and DBP > 100). Participants with missing blood pressure information at baseline (1990 in men and 1988 in women) were excluded from analyses of changes in blood pressure over time.

A question on serum cholesterol (within the previous 5 years) was first asked in the NHS cohort in 1988 and in the HPFS in 1986, but we used 1990 as baseline for both cohorts, because the range of reported values was expanded on the 1990 questionnaires and allowed for more accurate exposure assessment. Because of small numbers, participants who reported extreme levels of blood cholesterol were grouped together and assigned arbitrary a priori values (< 159 mg/dL = 159 mg/dL, >270 mg/dL = 270 mg/dL). Remaining participants were assigned the midpoint of the reported ranges, which included 159 to 179, 179 to 199, 199 to 219, and 219 to 269. Individuals reporting cholesterol-lowering drug use were assigned to the highest category of serum cholesterol (>270 mg/dL) or, to examine the robustness of the results, excluded from the analysis. No meaningful differences were observed for individuals with missing serum cholesterol (n = 53,732, 34.3%) compared with those who reported their serum cholesterol in regard to age, smoking history, body mass index (BMI), caffeine intake, and alcohol consumption. The validity of self-reported total cholesterol was examined in a subset of cohort participants whose cholesterol levels (measurements are a mix of fasting and nonfasting) were measured as part of a previous investigation. Serum measurements and self-reported total cholesterol values were available for 1,591 women and 1,790 men. Comparing

the self-reported values in 1990 with measured serum values resulted in Spearman correlation coefficients of 0.56 (women) and 0.44 (men) and regression coefficients of 0.54 (women) and 0.51 (men), all with corresponding p values < 0.001 . Further, self-reported total serum cholesterol is a predictor of myocardial infarction in these cohorts (unpublished data), similar to estimates reported using measured serum cholesterol.¹⁵

Covariate assessment

Information on smoking, weight, caffeine, alcohol, total energy intake, nonsteroidal anti-inflammatory drug (NSAID) use (including aspirin and non-aspirin NSAIDs), and physical activity was assessed via biennial questionnaires. BMI was calculated in kilograms per meter squared using height reported at baseline (1976 for women and 1986 for men) and updated weight. Validated food frequency questionnaires, which included information on caffeine intake, alcohol consumption, and total energy intake,¹⁶ were administered to women in 1980 and 1984 and to both cohorts in 1986 and every 4 years thereafter. Total physical activity was calculated in metabolic equivalent tasks (METs)¹⁷ and updated biennially (with the exception of 1990 in women) beginning in 1986.

Statistical analysis

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). Cox proportional hazards models were used to obtain RRs for the main effects adjusting for age (years) and smoking (quintiles of pack-years). Multivariate RRs were obtained from Cox proportional hazards models adjusting for age (years), smoking (quintiles of pack-years), caffeine intake (quintiles), total calorie intake (quintiles), alcohol consumption (quintiles), physical activity (METs), NSAID use (yes/no), and BMI (< 23 , 23 to 25, 25 to 27, 28 to 30, 30+). Resulting log RRs from men and women were pooled using the inverse of their variances. The fixed effects model was used as tests of heterogeneity were nonsignificant at the $\alpha = 0.05$ level.¹⁸

Detailed methods to examine temporal changes of exposures before and after PD diagnosis have been published previously.^{19,20} Briefly, we first calculated residuals of DBP or SBP by fitting a regression model with age, age squared, pack-years of smoking, and BMI as predictors, among all cohort participants and for each questionnaire cycle. By definition, the mean residual among all participants will be zero at each cycle, and the mean residual among cases will thus represent their average departure from the predicted values based on the entire cohort. The means of these residuals among individuals with PD were then plotted against time to the diagnosis (years before diagnosis: >8 , 6 to 8, 4 to 6, 2 to 4, 0.5 to 2, ± 6 months) or since the diagnosis (years after diagnosis: ± 6 months, 0.5 to 2, 2 to 4, 4 to 6, >6). The significance of changes in blood pressure over time among individuals with PD was tested by regressing the SBP (or DBP) on time since diagnosis as a continuous variable. We examined both the overall trend and separately the trend before and after the date of PD diagnosis.

RESULTS

During the follow-up period, there were 530 incident cases of PD, including 264 in women (average age at diagnosis of 63.5 years) and 266 cases in men (average age at diagnosis of 69.7 years). Individuals with history of hypertension, hypercholesterolemia, and diabetes, as expected, were less physically active and had higher BMIs than those without these conditions (table 1).

Overall, risk of PD was not associated with the updated history of high cholesterol, hypertension, or diabetes (table 2). Age- and smoking-adjusted RRs (95% CIs) were also

nonsignificant for baseline history of high cholesterol (RR = 1.29, 95% CI = 0.98 to 1.69), hypertension (RR = 0.99, 95% CI = 0.80 to 1.23), or diabetes (RR = 1.12, 95% CI = 0.69 to 1.81). Results were similar in analyses further adjusted for caffeine and alcohol intake, NSAID use, physical activity, total energy intake, and BMI, or when history of hypertension, high cholesterol, and diabetes were simultaneously included in the Cox regression model. Subanalyses among ever smokers and never smokers did not result in any significant associations either in men or women. We also found no associations between updated history of use of antihypertensive drugs (age- and smoking-adjusted RR for ever users as compared with never users = 1.15, 95% CI = 0.95 to 1.39) or cholesterol-lowering medication (age- and smoking-adjusted RR for ever users as compared with never users = 0.85, 95% CI = 0.59 to 1.23) and risk of PD; results were similar using baseline information on drug use and in multivariate models.

Self-reported total cholesterol in 1990 (because of missing values, this result is based on 141 incident cases in women and 173 in men) was associated with a decreased risk of PD (RR for a 50-mg/dL increase in total cholesterol = 0.86, 95% CI = 0.78 to 0.95, *p* for trend = 0.02). Analyses stratified by sex revealed a modest but significant trend of decreasing PD risk with increasing cholesterol in women but not in men (table 3). When analyzed as a continuous variable, every 50-mg/dL increase in total cholesterol was associated with an 18% lower risk of PD in women (RR = 0.82, 95% CI = 0.68 to 0.99, *p* for trend = 0.04) but only a 10% lower risk in men (RR = 0.90; 95% CI = 0.76 to 1.05, *p* for trend = 0.19). Among men, although no significant association between increasing cholesterol and risk of PD was observed, men with the highest total cholesterol (>270 mg/dL) had a significantly lower risk of PD when compared with men with the lowest total cholesterol (<159 mg/dL) (RR = 0.36, 95% CI = 0.17 to 0.80, *p* = 0.01; table 3). Similar results were obtained when cholesterol-lowering medication users were excluded from the analysis.

Overall, in analyses adjusted for age, pack-years of smoking, and BMI, the average values for SBP among individuals with PD were similar to those of individuals without PD before the diagnosis, but declined thereafter (*p* = 0.02; figure). However, this downward trend was no longer significant in analyses excluding users of antihypertensive medications. In contrast, no significant trends were observed for DBP, either before or after the diagnosis of PD.

DISCUSSION

In this large prospective investigation, we found no association between history of hypertension, hypercholesterolemia, or diabetes and risk of PD. These results are consistent with those of some previous studies,^{5,6,8} but not others in which a history of hypertension^{6,7,9} or diabetes^{9,10} was associated with a decreased risk of PD. The inconsistency may be partially due to the retrospective exposure assessment of these conditions and the ambiguous time period of exposure classification in many of these studies. In a recent case-control study, a 40% lower risk of PD was estimated among subjects with diabetes, and a significant interaction between smoking status and diabetes was found among men but not women.¹⁰ In contrast, in a cohort study in Finland, risk of PD was 85% higher in men and women with Type 2 diabetes.²¹ However, we did not find an association between diabetes and risk of PD in either men or women and additional analyses restricted to nonsmokers or smokers did not suggest any differential effect.

Strengths of the current study include the large sample size, the prospective design, the high rate of follow-up, the availability of detailed and validated information on cigarette smoking and others potential confounders, and the multiple updated assessments of the exposures of interest, which provide a clear temporal sequence between vascular factors and PD diagnosis. PD patients may exhibit autonomic dysfunction,^{22,23} and changes in weight²⁰ and physical

activity¹⁹ have been documented to occur before diagnosis and could cause secondary changes in blood pressure, cholesterolemia, and risk of diabetes. To determine whether these conditions are risk factors for PD, it is therefore important that their presence is established before the onset of neurologic symptoms, and preferably several years earlier.

There are, however, some potential limitations. Exposures were assessed through self-reported doctor-diagnosed disease, rather than by direct clinical examinations. Although the use of self-reported history of hypertension, diabetes, and cholesterol has been validated,^{13,14} some misclassification may still occur. This would likely be nondifferential and may have attenuated possible existing relationships. However, the findings that self-reported history of hypertension, hypercholesterolemia, and diabetes are strong predictors of heart disease and stroke^{13,24} and self-reported total blood cholesterol predicts myocardial infarction (unpublished data) provide evidence of validity of the reported exposures and suggest that bias due to misclassification is likely to be modest. Some misclassification in PD diagnosis is also expected, but error from this source is also likely to be small. In recent clinicopathologic studies, the positive predictive value of clinical PD diagnosis was approximately 90% for diagnoses made by general neurologists²⁵ and even higher for diagnoses made by movement disorder specialists.²⁶ Finally, as in all observational studies, unmeasured confounding cannot be excluded, but it seems unlikely that this could account for the null results. All of the analyses were adjusted for the strongest risk factors for PD, including sex, age, and smoking history, the latter based on detailed, prospectively collected, and validated information. The role of other potential confounders, such as caffeine, alcohol consumption, BMI, physical activity, and use of NSAIDs were examined in multivariate models and were found to have little impact on effect estimates.

Average SBP and DBP among individuals who developed PD were similar to those of individuals without PD throughout the study period, which extended from 10 years before diagnosis to 8 years after diagnosis, except for a small but significant decline in SBP after the diagnosis. This decrease in SBP after diagnosis is consistent with the observation that autonomic dysregulation may be associated with PD in some patients^{22,23} and may increase with disease severity.^{27,28} Additionally, L-dopa and other treatments may result in resting hypotension, increased orthostatic hypotension, and increased autonomic dysfunction independent of disease severity.^{22,27,29–31} However, the trend of decreasing SBP after PD diagnosis was attenuated after exclusion of those on antihypertensive medications, and may thus reflect in part a stronger response to treatment of SBP in individuals with PD. Additionally, this trend after diagnosis may contribute to explain the decreased prevalence of measured hypertension in studies among diagnosed PD cases.

There was a suggestion of a potential protective effect of increasing total cholesterol, which was stronger in women than in men. These results should be interpreted with caution because the results were only marginally significant and could have occurred by chance. However, this finding is consistent with the report of lower levels of LDL cholesterol among patients with PD than controls³² and with the results of a recent prospective study of serum cholesterol levels and risk of PD in which a protective effect of increasing cholesterol was observed in women but not in men.³³ Further investigation of the potential protective effect of high cholesterol and PD is nevertheless warranted, particularly because in this study we did not have individual information on specific cholesterol fractions. Of interest, plasma levels of uric acid have been found to be strongly inversely related to risk of PD,^{34–36} it would thus be important in future investigations to consider possible confounding by uricemia.

Overall, the results of this large prospective study do not support a role for hypertension, diabetes, or high total cholesterol as risk factors for PD. A possible decreased risk of PD

associated with high plasma cholesterol, particularly in women, cannot be excluded and deserves further investigation.

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GLOSSARY

ACE	angiotensin-converting enzyme
BMI	body mass index
DBP	diastolic blood pressure
HPFS	Health Professionals Follow-up Study
METS	metabolic equivalent tasks
NHS	Nurses' Health Study
NSAID	nonsteroidal anti-inflammatory drug
PD	Parkinson disease
RR	relative risk
SBP	systolic blood pressure

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Figure.

Means and 95% CIs of differences between observed and expected blood pressure (DBP and SBP) of PD cases adjusting for age, age squared, and BMI, plotted in relation to time of diagnosis

Sample sizes in order of time points for systolic blood pressure (SBP) are 82, 140, 176, 216, 140, 108, 102, 91, 54, and 29, and those for diastolic blood pressure (DBP) are 81, 129, 142, 170, 109, 88, 83, 77, 51, and 29. The time points at 8 years after diagnosis for both DBP and SBP include only female participants—no men had adequate follow-up data at 8 years after diagnosis. p for trend for SBP after diagnosis = 0.02. Mean residual DBP among Parkinson disease (PD) cases at 1.3 and 5 years after diagnosis was significantly lower than that among

individuals without PD ($p = 0.005$ and 0.01 , respectively); however, the trend in DBP after diagnosis was not significant. BMI = body mass index.

Table 1

Baseline * characteristics according to hypertension, high cholesterol, or diabetes history

	Hypertension		High cholesterol		Diabetes	
	Yes	No	Yes	No	Yes	No
Women	n = 13,895	n = 107,151	n = 3,981	n = 117,065	n = 2,155	n = 118,891
Age, y	46.1	42.0	46.4	42.3	45.3	42.4
Current smokers, %	32.0	33.5	35.7	33.2	31.5	33.3
Past smokers, %	25.0	23.1	24.7	23.3	23.9	23.3
Caffeine intake, mg/day [†]	356.1	395.2	370.5	391.5	368.5	391.0
Alcohol consumption, g/day [†]	6.7	6.4	6.0	6.4	3.7	6.4
Physical activity (MET) [‡]	12.6	14.3	12.8	14.1	13.0	14.1
BMI, kg/m ²	26.4	23.4	25.1	23.7	27.1	23.7
Energy intake, kcal/day [‡]	1,563	1,567	1,538	1,567	1,602	1,566
NSAID use, % [§]	46.0	48.4	46.9	48.2	46.7	48.1
Men	n = 11,283	n = 39,550	n = 6,450	n = 44,383	n = 1,604	n = 49,229
Age, y	58.6	53.6	57.1	54.4	60.8	54.5
Current smokers, %	9.9	9.7	8.7	9.8	10.5	9.6
Past smokers, %	45.2	41.0	46.0	41.3	47.6	41.8
Caffeine intake, mg/day	212.2	232.0	206.6	230.3	233.5	227.1
Alcohol consumption, g/day	13.2	11.4	12.1	11.8	8.4	11.9
Physical activity (MET)	18.4	21.6	20.3	21.0	16.1	21.1
BMI, kg/m ²	26.0	24.7	25.4	24.9	25.6	24.9
Energy intake, kcal/day	1,957	1,994	1,950	1,991	1,958	1,987
NSAID use, %	38.7	30.8	41.9	31.2	37.6	32.5

Other than age, all variables were standardized to the age distributions of the cohorts.

* 1986 for men and 1976 for women. Values not reported at baseline are noted.

[†]Values in 1980, the first year in which nutrient data was reported for women.

[‡]Values in 1986, the first year in which physical activity was reported for women.

[§]Values in 1990, the first year in which aspirin and other nonsteroid anti-inflammatory drugs (NSAIDs) were all reported in women.

MET = metabolic equivalent task; BMI = body mass index.

Table 2

Relative risk of PD according to updated history of hypertension, diabetes, or high cholesterol

	No. of cases	Person-years	RR (95% CI)*	p Value
Hypertension				
Yes	195	904,853	0.96 (0.80–1.15)	0.63
No	335	2,504,018		
High cholesterol				
Yes	193	834,165	0.98 (0.82–1.19)	0.86
No	337	2,574,707		
Diabetes				
Yes	37	150,256	1.04 (0.74–1.46)	0.81
No	493	3,258,616		

* Estimates were adjusted for age and smoking status (quintiles of pack-years).

PD = Parkinson disease; RR = relative risk.

Table 3
Relative risk of PD associated with self-reported total serum cholesterol

Total cholesterol, mg/dL	No. of cases	Person-years	RR (95% CI) [*]	<i>p</i> Value
Women (n = 141 cases) [†]				
< 159	13	85,109		
159–179	17	82,313	1.38 (0.67–2.85)	0.38
179–199	28	107,924	1.58 (0.82–3.04)	0.18
199–219	26	144,698	0.96 (0.49–1.86)	0.90
219–269	49	188,113	1.24 (0.67–2.28)	0.50
270 +	8	64,266	0.54 (0.22–1.30)	0.17
				$\chi^2 = -2.08$ <i>p</i> for trend = 0.04
Men (n = 173) [‡]				
< 159	27	38,238		
159–179	20	42,245	0.64 (0.36–1.15)	0.14
179–199	35	60,639	0.78 (0.47–1.29)	0.33
199–219	33	63,238	0.69 (0.42–1.15)	0.15
219–269	50	64,281	1.02 (0.64–1.63)	0.94
270 +	8	27,423	0.36 (0.17–0.80)	0.01
				$\chi^2 = -1.32$ <i>p</i> for trend = 0.19

* Estimates were adjusted for age and smoking status (quintiles of pack-years), and baseline is 1990.

[†] Thirty-seven cases in women were missing self-reported serum cholesterol information.

[‡] Forty-seven cases in men were missing self-reported serum cholesterol information.

PD = Parkinson disease; RR = relative risk.