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Metabolic Markers or Conditions Preceding Parkinson's Disease: A Case-Control Study

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Abstract

Background—Several metabolic markers or conditions have been explored as possible risk or protective factors for Parkinson's disease (PD); however, results remain conflicting. We further investigated these associations using a case-control study design.

Methods—We used the medical records-linkage system of the Rochester Epidemiology Project to identify 196 subjects who developed PD in Olmsted County, MN, from 1976 through 1995. Each incident case was matched by age (± 1 year) and sex to a general population control. We reviewed the complete medical records of cases and controls in the medical records-linkage system to abstract information about body mass index (BMI), cholesterol levels, hypertension, and diabetes mellitus preceding the onset of PD (or the index year).

Results—There were no significant differences between cases and controls for the metabolic markers or conditions investigated. No significant associations were found using 2 cut-offs for BMI levels (BMI ≥ 25 or BMI ≥ 30 kg/m²) and 3 cut-offs for cholesterol levels (> 200 , > 250 , or > 300 mg/dl). A diagnosis of hypertension or the documented use of anti-hypertensive medications were not significantly associated with the subsequent risk of PD (odds ratio [OR], 1.00; 95% confidence interval [CI], 0.65–1.54; $P = .99$), nor was a diagnosis of diabetes mellitus or the use of glucose-lowering medications (OR, 0.77; 95% CI, 0.37–1.57; $P = .47$).

Conclusions—Our study, based on historical information from a records-linkage system, does not support an association between BMI, cholesterol levels, hypertension, or diabetes mellitus and later development of PD.

Keywords

Parkinson's disease; body mass index; cholesterol level; hypertension; diabetes mellitus

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Several metabolic markers or conditions have been explored as possible risk or protective factors for Parkinson's disease (PD).¹ Of relevance, mid-life elevations of body mass index (BMI), cholesterol levels, blood pressure, and glucose have been suggested as risk factors for Alzheimer's disease.² However, the existing data for PD remain controversial because of methodological differences across studies, sample size limitations, and potential dietary and genetic confounders. A recent review of risk factors for PD concluded that the role of metabolic conditions remains uncertain.¹ To further explore these associations, we investigated BMI, cholesterol levels, hypertension, and diabetes mellitus preceding the onset of PD in a case-control study using a records-linkage system.^{3, 4}

Methods

Cases

We used the medical records-linkage system of the Rochester Epidemiology Project to identify all subjects residing in Olmsted County, MN, who developed PD from 1976 through 1995. Details about the study population and the identification of incident cases were reported elsewhere.³⁻⁵ Our diagnostic criteria included 2 steps: the definition of parkinsonism as a syndrome and the definition of PD within the syndrome. Parkinsonism was defined as the presence of at least 2 of 4 cardinal signs: rest tremor, bradykinesia, rigidity, and impaired postural reflexes. PD was defined as the presence of parkinsonism with all 3 of the following criteria: 1) No other cause (e.g., repeated stroke with step-wise progression; repeated head injury; history of encephalitis; neuroleptic treatment within 6 months before onset; hydrocephalus; brain tumor). 2) No documentation of unresponsiveness to levodopa at doses of at least 1 gm/day in combination with carbidopa (applicable only to patients who were treated). 3) No prominent or early (within 1 year of onset) signs of more extensive nervous system involvement (e.g., dementia or dysautonomia), not explained otherwise.⁵ Our clinical classification of patients with PD through medical records review was found to be valid compared with a direct examination by a movement disorders specialist, as reported elsewhere.⁶ Onset of PD was defined as the year in which a cardinal sign of PD was first noted by the patient, by family members, or by a care provider (as recorded in the medical record).

Controls

Each case was individually matched by age (± 1 year) and sex to a general population control residing in Olmsted County and free of PD, other parkinsonism, or tremor of any type in the index year (year of onset of PD in the matched case). The list of all county residents from which potential controls were randomly drawn was provided by the records-linkage system.^{3, 4} This list has been shown to be complete by comparison with a random-digit-dialing telephone sample and with the census.^{3, 4} Records of potential controls were reviewed by a neurologist (not an author) to exclude the presence of PD, other types of parkinsonism, or tremor of any type before or during the index year. The presence of dementia or other neurologic diseases was not an exclusion criterion. Our exclusion of parkinsonism in controls through medical record review was found to be valid compared with a direct examination by a movement disorders specialist, as reported elsewhere. Further details about the identification of controls were reported elsewhere.⁶

Ascertainment of metabolic markers or conditions

The complete medical records of cases and controls before the onset of PD or the index year were reviewed by a neurologist (R.S.). To avoid a possible bias in defining the metabolic conditions (exposure suspicion bias),⁷ we only considered diagnoses that were given by the care giving physician at the time of medical evaluation. We did not assign new diagnoses and did not modify the historical diagnoses based on current criteria or practices. Only

metabolic markers or conditions documented in the medical records before the index year were accepted as exposures. Subjects with no information about the metabolic markers or conditions of interest before the index year were considered unexposed.

We abstracted data on weight and height from medical records to compute BMI in kg/m^2 . Because height and weight were measured virtually at every medical visit, we only collected values closest to age 20 years, at subsequent visits nearest to decade birthdays (e.g., age 30, 40, 50 years), and at the visit nearest to the onset of PD or index year. We used 2 alternative cut-off values: at least one BMI $\geq 25 \text{ kg/m}^2$ or at least one BMI $\geq 30 \text{ kg/m}^2$.⁸

We abstracted total cholesterol levels in chronological order starting from the first available record through the onset of PD or the index year. Because some subjects had a large number of cholesterol values over their full life spans, we abstracted the values approximately every 2 years from the first available measure through the index year. If the lag time between the measures was greater than 2 years, the next closest available cholesterol level was abstracted. As a measure of severity of hypercholesterolemia, we also collected information on the use of statins; however, this proved of limited value because statins were rarely prescribed before 1995. To explore a possible threshold effect, we investigated 3 alternative cut-off levels for blood cholesterol: at least one level $> 200 \text{ mg/dl}$, at least one level $> 250 \text{ mg/dl}$, or at least one level $> 300 \text{ mg/dl}$.⁹

Hypertension was defined as a diagnosis reported by a physician in the medical records or as use of anti-hypertensive medications. All information about anti-hypertensive medication use was abstracted, and the class of medication was noted (thiazides, loop diuretics, potassium-sparing agents, alpha-methyldopa, adrenergic agonists, hydralazine, minoxidil, sodium nitroprussiate, beta-blockers, etc.). Subjects who never received a diagnosis of hypertension in the medical record, but to whom anti-hypertensive treatment was prescribed (without other plausible indication) were considered to have had hypertension.

Diabetes mellitus was defined as a diagnosis reported by a physician in the medical records or as use of glucose-lowering medications. As a measure of severity, we also collected information about diabetic treatments (diet, oral therapy, insulin, etc.).

The study was approved by the institutional review boards of the Mayo Clinic and of Olmsted Medical Center. Written informed consent was not required for passive medical record review.⁴

Reliability of Exposure Information

To test the reliability of our ascertainment of metabolic markers and conditions, a second physician (not an author) reviewed and abstracted a random sample of 20 subjects (5% of the total sample). He was kept unaware of the case or control status of subjects and of the data abstracted by the primary data abstractor (R.S.). Inter-rater reliability was high for all 4 metabolic markers and conditions. In particular, the two abstractors had 80% agreement with κ value of 0.54 (95% CI, 0.19–0.90) for BMI $\geq 25 \text{ kg/m}^2$; 95% agreement with a κ value of 0.89 (95% CI, 0.69–1.00) for total cholesterol $> 200 \text{ mg/dl}$; 90% agreement with κ value of 0.74 (95% CI, 0.40–1.00) for hypertension; and 100% agreement with κ value of 1.0 for diabetes mellitus.

Statistical Analysis

Consistent with the matched design, matched-pairs analyses were performed, and the odds ratio (OR) was used to estimate the relative risk. For each risk factor, we calculated an OR, a 95% confidence interval (CI), and a *P* value (2-tailed test with $\alpha = 0.05$) using conditional logistic regression.^{10, 11} We performed separate analyses using 2 progressively increasing

cut-offs for BMI (≤ 25 or ≥ 30 kg/m²) and 3 progressively increasing cut-offs for total cholesterol (> 200 , > 250 , or > 300 mg/dl).

Analyses were conducted in the overall sample and also in men and women separately to explore possible sex differences. Analyses were also stratified by age at onset of PD (≤ 71 vs > 71 years; median cut-off) and for PD with or without rest tremor.¹² To investigate timing effects, we considered 2 strata for exposures proximate to index year or distant from the index year. For BMI, we used the cut-off of 20 years (0–19 years before the index year and ≥ 20 years). For cholesterol levels, hypertension, and diabetes mellitus, we used the cut-off of 10 years (0–9 years before the index year and ≥ 10 years). These cut-offs were approximately the median of the distribution among controls.

Analyses were repeated using regression models that also included cigarette smoking (ever vs. never) and coffee consumption (ever vs. never) as potential confounders. These analyses ignored the matching but we adjusted for age (continuous variable) and sex. Information about smoking and coffee consumption was available from a previous study.¹³ All analyses were performed using SAS® version 9.2 (SAS Institute, Cary, NC).

Results

We identified 202 patients who developed PD from 1976 through 1995 (incident cases). These patients were matched by age and sex with 202 controls. However, 6 individuals (5 cases and 1 control) did not authorize the use of their medical records for research and the corresponding pairs could not be studied. Therefore, we included 196 case-control pairs for a total of 392 individuals. Among the cases, 121 (61.7%) were men and 75 (38.3%) were women; the median age at onset of PD was 71 years (range, 41–97 years). The distribution by age and sex was similar in controls due to the matched design. The median duration of enrollment in the records-linkage system preceding the index year was 38 years (range, 2–73 years) for cases and 38 years (range, < 1 –73 years) for controls (Wilcoxon signed rank test, $P = .35$).

Table 1 shows the results of our case-control analyses for BMI and cholesterol levels. No BMI measurements were available for 19 controls (9.7%) and 9 cases (4.6%), and these persons were considered to be unexposed in the analyses (normal BMI). None of the analyses for BMI reached statistical significance overall, in men and women separately, in analyses stratified by time before the index year, or in analyses adjusted for cigarette smoking and coffee consumption (Table 1). In addition, no associations were found in strata by age at onset of PD or by the presence of rest tremor (data not shown). Finally, the median weight loss per year preceding the index year was similar in cases and controls (data not shown). Sensitivity analyses excluding cases and controls without any BMI measurement preceding the index year yielded similar results. In particular, the OR was 1.06 (95% CI, 0.66–1.70; $P = .80$) for BMI ≤ 25 kg/m² and 1.20 (95% CI, 0.75–1.91; $P = .46$) for BMI ≥ 30 kg/m².

No cholesterol measurements were available for 61 controls (31.1%) and 55 cases (28.1%), and these persons were considered to be unexposed in the analyses (normal cholesterol). None of the analyses for cholesterol reached statistical significance overall, in men and women separately, in analyses stratified by time before the index year, or in analyses adjusted for cigarette smoking or coffee consumption (Table 1). In addition, no associations were found in strata by age at onset of PD or by the presence of rest tremor (data not shown). In a logistic regression model considering the highest cholesterol level for each person as a continuous variable, the OR was 1.04 for each increase of 10 mg/dl (95% CI, 0.99 – 1.09; $P = .15$; analyses ignoring the matching but adjusted by age and sex).

Sensitivity analyses excluding cases and controls without any cholesterol measurement preceding the index year yielded similar results. In particular, the OR was 1.11 (95% CI, 0.59-2.09; $P = .75$) for cholesterol > 200 mg/dl, 1.38 (95% CI, 0.84-2.25; $P = .20$) for cholesterol > 250 mg/dl, and 1.40 (95% CI, 0.69-2.87; $P = .35$) for cholesterol > 300 mg/dl.

Table 2 shows the results of our case-control analyses for hypertension and diabetes mellitus. No significant difference was observed between cases and controls for hypertension in the overall analysis, in men and women separately, in analyses stratified by time before the index year, or in analyses adjusted for cigarette smoking or coffee consumption (Table 2). In addition, no associations were found in strata by age at onset of PD or by presence of rest tremor (data not shown). Finally, no associations were found in analyses considering thiazides, loop diuretics, and potassium-sparing agents separately (data not shown). No data were available for calcium channel blockers because our study time frame preceded their introduction in clinical practice.

There was no significant difference between cases and controls for diabetes mellitus in the overall analysis, in men and women separately, in analyses stratified by time before the index year, or in analyses adjusted for cigarette smoking or coffee consumption (Table 2). In addition, no associations were found in strata by age at onset of PD or by presence of rest tremor (data not shown).

Discussion

Our study failed to support the hypothesis that certain metabolic markers or conditions affect the risk of PD. Our results were similar in strata defined by sex, time before the index year, age at onset of PD, or by presence of rest tremor.

Several studies have investigated the association between BMI and the risk of PD. Triceps skin fold thickness measured in mid-life was associated with an increased risk of PD in the Honolulu Aging Study.¹⁴ Similarly, increased BMI was associated with an increased risk of PD independent of other risk factors in a Finnish study,¹⁵ and abdominal obesity increased the risk of PD among non-smokers in the Nurses' Health Study.¹⁶ By contrast, the association of BMI with PD was not confirmed in the Health Professional Follow-up Study or in the Nurses' Health Study overall.¹⁶ In addition, in a recent study from the Cancer Prevention Study II Nutrition Cohort, neither BMI nor waist circumference was associated with PD.¹⁷ Similarly, we did not confirm the association between BMI and PD using historical data from a records-linkage system.

Hypercholesterolemia was associated with a reduced risk of PD in women in one population-based study.¹⁸ By contrast, high cholesterol levels were associated with an increased risk of PD in another study.¹⁹ A third large cohort study showed no association between self-reported hypercholesterolemia or use of cholesterol-lowering drugs and PD; however, the risk decreased as the level of self-reported cholesterol increased.²⁰ Our study revealed no association between cholesterol levels and PD.

Caution should be used when interpreting our findings for BMI and cholesterol as evidence for absence of an association. Indeed, all of the ORs reported in Table 1 were greater than 1.0, and some ORs were compatible with a sizeable association. We also observed a suggestive trend of higher OR with longer length of exposure for both BMI and cholesterol. Finally, we observed higher ORs with higher cut-off levels for both BMI and cholesterol. Thus, our failure to detect significant associations may be due to sample size limitations. For example, our analysis for BMI ≥ 30 kg/m² occurring ≥ 20 years before index had only 80% power to detect an OR of 2.39 or greater. Similarly, our analysis for cholesterol > 300 mg/dl occurring ≥ 10 years before index had only 80% power to detect an OR of 3.03 or greater.

A case-control study showed an increased risk of PD in women with a medical records history of hypertension,²¹ but this association was not confirmed in a larger cohort study.²⁰ In a recent Japanese case-control study, hypertension was associated with a reduced risk of PD.²² We did not observe any significant difference between cases and controls for hypertension reported in medical records or for any class of anti-hypertension medications. However, the most common drugs used in our population at the time of the study were thiazides, loop diuretics, and potassium-sparing agents. One study suggested that isradipine, a drug in the dihydropyridines family, may be protective for PD because it crosses the blood brain barrier and acts on the L-type calcium channels in the brain.²³ Unfortunately, we were unable to explore the specific association between PD and isradipine because the drug was not available in the study years.

Diabetes mellitus has been reported as a possible risk factor for PD in a cohort study from Finland,²⁴ but the association was not confirmed in another U.S. study.²⁰ Conversely, two case-control studies have reported that subjects with diabetes mellitus had a lower risk of PD.^{21, 25} A recent study from the Cancer Prevention Study II Nutrition Cohort did not evidence any association between diabetes and PD.¹⁷ Similarly, our study based on a records-linkage system yielded no association between diabetes mellitus and PD.

Our study has a number of strengths. First, it was based on a series of incident cases of PD and on well-defined general population controls, thus reducing referral bias and incidence-prevalence bias.⁷ Second, we were able to avoid recall bias by considering diagnoses that were historically documented in medical records before the onset of PD (or the index year).⁷ Third, we explored possible difference in associations between men and women. Fourth, the use of historical records in the medical records-linkage system facilitated the study of metabolic markers or conditions that were documented several decades prior to the motor onset of PD. This time frame was important to explore possible cause-effect inversions.

On the other hand, the study has several limitations. First, it is possible that some cases or controls were treated for metabolic conditions at a medical facility outside of the medical records-linkage system, and these conditions were not documented in the system. However, both cases and controls had a median enrollment in the records-linkage system of approximately 40 years, and any loss of information should be symmetric (non-differential misclassification). Second, we did not have information on dietary factors that may modify the metabolic markers or conditions considered in this study. However, we were able to conduct multivariable analyses including cigarette smoking and coffee consumption. Third, some of the exposures were relatively rare (e.g., diabetes mellitus), and our study had limited power.

In conclusion, several studies have reported an association between metabolic markers or conditions and PD; however, our study based on a records-linkage system failed to support an association of BMI, cholesterol levels, hypertension, or diabetes mellitus with risk of PD. Further studies are needed to clarify the existing conflicting evidence.

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References

1. Elbaz A, Moisan F. Update in the epidemiology of Parkinson's disease. *Curr Opin Neurol*. 2008; 21(4):454–460. [PubMed: 18607207]
2. Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. *Biol Psychiatry*. 2010; 67(6):505–512. [PubMed: 19358976]

3. Melton LJ 3rd. History of the Rochester Epidemiology Project. *Mayo Clin Proc.* 1996; 71(3):266–274. [PubMed: 8594285]
4. St Sauver JL, Grossardt BR, Yawn BP, Melton LJ 3rd, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester Epidemiology Project. *Am J Epidemiol.* 2011; 173(9):1059–1068. [PubMed: 21430193]
5. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976–1990. *Neurology.* 1999; 52(6):1214–1220. [PubMed: 10214746]
6. Elbaz A, Peterson BJ, Yang P, et al. Nonfatal cancer preceding Parkinson's disease: a case-control study. *Epidemiology.* 2002; 13(2):157–164. [PubMed: 11880756]
7. Sackett DL. Bias in analytic research. *J Chronic Dis.* 1979; 32(1-2):51–63. [PubMed: 447779]
8. National Institutes of Health. NIH Roadmap for Medical Research: Roadmap Initiatives. 2011
9. American Heart Association. What Your Cholesterol Levels Mean. American Heart Association; Dallas: 2010.
10. Breslow NE, Day NE. Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ.* 1980; 32:5–338. [PubMed: 7216345]
11. Szklo, M.; Nieto, FJ. *Epidemiology: Beyond the Basics.* Aspen; Gaithersburg, MD: 2000.
12. Elbaz A, Bower JH, Peterson BJ, et al. Survival study of Parkinson disease in Olmsted County, Minnesota. *Arch Neurol.* 2003; 60(1):91–96. [PubMed: 12533094]
13. Benedetti MD, Bower JH, Maraganore DM, et al. Smoking, alcohol, and coffee consumption preceding Parkinson's disease: a case-control study. *Neurology.* 2000; 55(9):1350–1358. [PubMed: 11087780]
14. Abbott RD, Ross GW, White LR, et al. Midlife adiposity and the future risk of Parkinson's disease. *Neurology.* 2002; 59(7):1051–1057. [PubMed: 12370461]
15. Hu G, Jousilahti P, Nissinen A, Antikainen R, Kivipelto M, Tuomilehto J. Body mass index and the risk of Parkinson disease. *Neurology.* 2006; 67(11):1955–1959. [PubMed: 17159100]
16. Chen H, Zhang SM, Schwarzschild MA, Hernan MA, Willett WC, Ascherio A. Obesity and the risk of Parkinson's disease. *Am J Epidemiol.* 2004; 159(6):547–555. [PubMed: 15003958]
17. Palacios N, Gao X, McCullough ML, et al. Obesity, diabetes, and risk of Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society.* 2011; 26(12):2253–2259. [PubMed: 21739472]
18. de Lau LML, Koudstaal PJ, Hofman A, Breteler MMB. Serum cholesterol levels and the risk of Parkinson's disease. *Am J Epidemiol.* 2006; 164(10):998–1002. [PubMed: 16905642]
19. Hu G, Antikainen R, Jousilahti P, Kivipelto M, Tuomilehto J. Total cholesterol and the risk of Parkinson disease. *Neurology.* 2008; 70(21):1972–1979. [PubMed: 18401018]
20. Simon KC, Chen H, Schwarzschild M, Ascherio A. Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. *Neurology.* 2007; 69(17):1688–1695. [PubMed: 17761552]
21. Powers KM, Smith-Weller T, Franklin GM, Longstreth JWT, Swanson PD, Checkoway H. Diabetes, smoking, and other medical conditions in relation to Parkinson's disease risk. *Parkinsonism Relat Disord.* 2006; 12(3):185–189. [PubMed: 16364673]
22. Miyake Y, Tanaka K, Fukushima W, et al. Case-control study of risk of Parkinson's disease in relation to hypertension, hypercholesterolemia, and diabetes in Japan. *J Neurol Sci.* 2010; 293(1-2):82–86. [PubMed: 20347450]
23. Ritz B, Rhodes SL, Qian L, Schernhammer E, Olsen JH, Friis S. L-type calcium channel blockers and Parkinson disease in Denmark. *Ann Neurol.* 2010; 67(5):600–606. [PubMed: 20437557]
24. Hu G, Jousilahti P, Bidel S, Antikainen R, Tuomilehto J. Type 2 diabetes and the risk of Parkinson's disease. *Diabetes Care.* 2007; 30(4):842–847. [PubMed: 17251276]
25. D'Amelio M, Ragonese P, Callari G, et al. Diabetes preceding Parkinson's disease onset. A case-control study. *Parkinsonism Relat Disord.* 2009; 15(9):660–664.

TABLE 1
Association between Parkinson's disease and increased body mass index or hypercholesterolemia (196 cases and 196 controls)

Risk or protective factor	Exposure frequency		Discordant pairs ^d		Concordant pairs ^d		Unadjusted Analyses ^b		Adjusted Analyses ^c	
	Cases no. (%)	Controls no. (%)	+/-	-/+	+/+	-/-	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Body mass index (BMI)										
BMI 25 kg/m ²	139 (70.9)	129 (65.8)	51	41	88	16	1.24 (0.83-1.88)	.30	1.18 (0.74-1.88)	.49
BMI 30 kg/m ²	52 (26.5)	43 (21.9)	38	29	14	115	1.31 (0.81-2.13)	.27	1.26 (0.77-2.07)	.35
Men	32 (26.5)	28 (23.1)	22	18	10	71	1.22 (0.66-2.28)	.53	1.03 (0.55-1.96)	.92
Women	20 (26.7)	15 (20.0)	16	11	4	44	1.46 (0.68-3.13)	.34	1.59 (0.68-3.68)	.28
No increased BMI	144 (73.5)	153 (78.1)	--	--	--	--	1.00 (reference)	--	1.00 (reference)	--
0-19 years before index	26 (13.3)	25 (12.8)	--	--	--	--	1.12 (0.62-2.02)	.72	1.03 (0.54-1.97)	.93
20 years before index	26 (13.3)	18 (9.2)	--	--	--	--	1.65 (0.82-3.32)	.16	1.57 (0.80-3.08)	.19
Cholesterol levels ^d										
Cholesterol > 200 mg/dl	118 (60.2)	111 (56.6)	48	41	70	37	1.17 (0.77-1.78)	.46	1.17 (0.76-1.82)	.47
Cholesterol > 250 mg/dl	64 (32.7)	54 (27.6)	43	33	21	99	1.30 (0.83-2.05)	.25	1.54 (0.96-2.45)	.07
Cholesterol > 300 mg/dl	21 (10.7)	15 (7.7)	20	14	1	161	1.43 (0.72-2.83)	.31	1.49 (0.73-3.04)	.28
Men	11 (9.1)	9 (7.4)	11	9	0	101	1.22 (0.51-2.95)	.66	1.34 (0.52-3.46)	.54
Women	10 (13.3)	6 (8.0)	9	5	1	60	1.80 (0.60-5.37)	.29	1.72 (0.55-5.35)	.35
No hypercholesterolemia	175 (89.3)	181 (92.4)	--	--	--	--	1.00 (reference)	--	1.00 (reference)	--
0-9 years before index	6 (3.1)	5 (2.6)	--	--	--	--	1.25 (0.38-4.10)	.72	1.07 (0.30-3.81)	.92
10 years before index	15 (7.7)	10 (5.1)	--	--	--	--	1.51 (0.68-3.38)	.31	1.70 (0.73-3.97)	.22

BMI, body mass index; CI, confidence interval.

^a (+/-) = matched pair with case exposed and control unexposed; (-/+) = matched pair with case unexposed and control exposed; (+/+) = matched pair with both case and control exposed; (-/-) = matched pair with both case and control unexposed.

^b Odds ratio from matched analyses.

^c Odds ratio from a regression model including cigarette smoking (ever vs. never) and coffee consumption (ever vs. never). These models ignored the matching but included age (continuous variable) and sex.

^d Mild, moderate, and severe hypercholesterolemia were defined using the American Heart Association 2010 guidelines.⁹ We also investigated the use of statins; however, statins were used before the index year by only 3 controls and 1 case. This low use of statins is consistent with the timeframe of our study (index years 1976 through 1995). In a logistic regression model considering cholesterol level as a continuous variable, the OR was 1.04 for each increase of 10 mg/dl (95% CI, 0.99 - 1.09; *P* = .15). These analyses ignored the matching but were adjusted by age (continuous variable) and sex.

TABLE 2
Association between Parkinson's disease and hypertension or diabetes mellitus (196 cases and 196 controls)

Risk or protective factor	Exposure frequency		Discordant pairs ^d		Concordant pairs ^d		Unadjusted Analyses ^b		Adjusted Analyses ^c	
	Cases no. (%)	Controls no. (%)	+/-	-/+	+/+	-/-	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Hypertension ^d	67 (34.2)	67 (34.2)	41	41	26	88	1.00 (0.65-1.54)	.99	0.99 (0.63-1.55)	.95
Men	43 (35.5)	39 (32.2)	31	27	12	51	1.15 (0.69-1.92)	.60	1.05 (0.59-1.88)	.86
Women	24 (32.0)	28 (37.3)	10	14	14	37	0.71 (0.32-1.61)	.42	0.83 (0.40-1.74)	.62
No hypertension	129 (65.8)	129 (65.8)	--	--	--	--	1.00 (reference)	--	1.00 (reference)	--
0-9 years before index	33 (16.8)	36 (18.4)	--	--	--	--	0.92 (0.53-1.58)	.75	0.81 (0.46-1.45)	.48
10 years before index	34 (17.4)	31 (15.8)	--	--	--	--	1.10 (0.63-1.94)	.74	1.21 (0.67-2.16)	.53
Diabetes mellitus ^e	13 (6.6)	17 (8.7)	13	17	0	166	0.77 (0.37-1.57)	.47	0.67 (0.31-1.48)	.32
Requiring the use of insulin	5 (2.6)	4 (2.0)	5	4	0	187	1.25 (0.34-4.66)	.74	1.46 (0.38-5.58)	.58
Men	7 (5.8)	12 (9.9)	7	12	0	102	0.58 (0.23-1.48)	.26	0.57 (0.21-1.56)	.28
Women	6 (8.0)	5 (6.7)	6	5	0	64	1.20 (0.37-3.93)	.76	1.05 (0.28-3.86)	.95
No diabetes mellitus	183 (93.4)	179 (91.3)	--	--	--	--	1.00 (reference)	--	1.00 (reference)	--
0-9 years before index	5 (2.6)	9 (4.6)	--	--	--	--	0.56 (0.19-1.66)	.29	0.51 (0.17-1.57)	.24
10 years before index	8 (4.1)	8 (4.1)	--	--	--	--	1.00 (0.38-2.66)	.99	0.88 (0.30-2.54)	.81

CI, confidence interval.

^a (+/-) = matched pair with case exposed and control unexposed; (-/+) = matched pair with case unexposed and control exposed; (++) = matched pair with both case and control exposed; (-/-) = matched pair with both case and control unexposed.

^b Odds ratio from matched analyses.

^c Odds ratio from a regression model including cigarette smoking (ever vs. never) and coffee consumption (ever vs. never). These models ignored the matching but included age (continuous variable) and sex.

^d Defined as a diagnosis of hypertension in the medical record or the use of anti-hypertensive medications. Analyses considering thiazides, loop diuretics, and potassium-sparing agents separately did not show significant associations.

^e Defined as a diagnosis of diabetes mellitus in the medical record or the use of glucose lowering medications.