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Do Risk Factors for Alzheimer's Disease Predict Dementia in Parkinson's Disease? An Exploratory Study

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Abstract: The extent to which concomitant Alzheimer's disease (AD) is etiologically related to the development of dementia in Parkinson's disease (PD) remains controversial. We explored the association of four risk factors associated with AD, including head injury, smoking, hypertension, and diabetes mellitus, with incident dementia in PD. A cohort of 180 nondemented PD patients from the Washington Heights community in northern Manhattan, New York, completed a risk factor questionnaire at baseline and was followed annually with neurological and neuropsychological evaluations. The association of baseline variables with incident dementia was analyzed by using Cox proportional hazards models. All analyses controlled for age at baseline, gender, years of education, duration of PD, and total Unified Parkinson's Disease Rating Scale (UPDRS) motor score at baseline. Of 180 patients (mean age, 71.0 ± 10.3 years), 52 (29%) became demented during a mean follow-up period of 3.6 ± 2.2 years. Head injury risk ratio ([RR] 0.9; 95% confidence interval [CI], 0.4–2.2; $P = 0.9$), hypertension (RR, 0.7; 95% CI, 0.4–1.4, $P = 0.3$), and diabetes mellitus (RR, 0.8; 95% CI, 0.3–2.3; $P = 0.7$) were not significantly associated with incident dementia in the Cox models. Patients who reported having ever smoked were at increased risk for the development of dementia compared with nonsmokers (RR, 2.0; 95% CI, 1.0–3.9; $P = 0.05$). Current smoking was significantly associated with incident dementia (RR, 4.5; 95% CI, 1.2–16.4; $P = 0.02$), whereas past smoking approached significance (RR, 1.9; 95% CI, 0.9–3.7; $P = 0.07$). Although an inverse association between smoking and PD has been reported in several studies, our study showed a positive association between smoking and dementia in the setting of PD. The association of smoking with incident dementia in PD deserves further study. © 2002 Movement Disorder Society

Key Words: Parkinson's disease; dementia; epidemiology; smoking

Previous prospective cohort studies have shown that demographic and clinical characteristics such as age, severity of extrapyramidal signs, depressive symptoms, levodopa-induced psychosis, and specific neuropsychological impairment are associated with an increased risk of developing dementia in patients with idiopathic Parkinson's disease (PD).[1–5] In a pilot case control study of risk factors for dementia in PD, a family history of dementia in first-degree relatives was reported significantly more often in the demented than in the nondemented PD group.[6] In another study, we reported an increased risk of Alzheimer's disease (AD) in siblings of demented PD patients compared with siblings of controls, supporting the possibility of familial aggregation of AD and PD dementia.[7] Few case control studies have explored the association of other risk factors, including environmental exposures and genetic influences, with PD dementia.[8–10]

The pathological substrate underlying cognitive impairment in PD has not been clearly defined, and it remains controversial to what extent concomitant AD is etiologically related to the development of dementia in PD. Clinical-pathological series have suggested that dementia in the setting of PD may be heterogeneous, involving either only subcortical pathology related to PD

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or subcortical pathology and additional cortical pathology, ie, cortical Lewy bodies and/or Alzheimer-type pathology.[11,12] Although shared risk factors do not necessarily suggest a common etiology, the demonstration that AD and PD dementia share a similar profile of risk factors could support the hypothesis of a common biological basis for AD and dementia in PD. On the other hand, the demonstration that the risk factors associated with AD are not associated with PD dementia would suggest that the two dementing processes do not have the same etiology, or alternatively, that only some of the patients with PD dementia have concomitant AD.

Several risk factors have been associated with cognitive decline in the elderly and dementia (or specifically AD), including *APOE4* genotype,[13] estrogen replacement therapy (inverse association),[14] head injury,[15–17] smoking,[18–20] hypertension,[21–23] and diabetes mellitus.[24–26] We and others have previously reported no association between the *APOE-ε4* allele and PD dementia,[27,28] a finding that does not support a common etiology for PD dementia and AD. We have also previously reported an inverse association between postmenopausal estrogen use and PD dementia compared with nondemented PD patients and controls,[29] which could support a common etiology for PD dementia and AD. In the present study, we evaluated the association of head injury, smoking, hypertension, and diabetes mellitus with incident dementia in a community-dwelling cohort of nondemented PD patients.

PATIENTS AND METHODS

A cohort of nondemented PD patients from the Washington Heights community in northern Manhattan, New York, was followed annually with neurological and neuropsychological evaluations. The ascertainment procedure and inclusion and exclusion criteria for the cohort have been previously described.[30] Patients were identified through the development of a "registry" for PD in the community for all individuals considered to have PD or a related disorder. This population-based PD cohort included, but was not restricted to, patients who received their care at the Columbia Presbyterian Medical Center. Idiopathic PD was defined according to clinical and research criteria.[31–33] Patients with postencephalitic and drug-induced parkinsonism or a Parkinson-plus syndrome were excluded, as were patients who presented memory loss or dementia before the motor manifestations of PD. Of 319 patients with idiopathic PD, 105 considered to be demented at baseline evaluation were excluded. Of 214 nondemented patients, 30 had no follow-up visit and 4 with signs or symptoms of stroke were excluded, leaving 180 patients for this analysis. Duration of PD was defined as the time period between the first symptom of PD and the baseline evaluation.

The annual clinical evaluation included the Unified Parkinson's Disease Rating Scale (UPDRS)[34] on all patients and the Hamilton Depression Rating Scale (HDRS)[35] on the majority of the patients. Past medical history was collected at every evaluation and included questions about whether the patient had hypertension and diabetes mellitus, when each one of these conditions was first diagnosed, its estimated duration, whether the patient had ever been treated, when the treatment started, and the patient's estimated compliance. The presence of other cardiovascular and systemic conditions was also elicited. The validity of this self-report/caregiver information compared with medical chart information has been examined in the same community.[36] The sensitivity was found to be good (>75%) for some conditions, including hypertension, valvular heart disease, angina, and stroke, but poor (<50%) for other conditions, including myocardial infarction, atrial fibrillation, congestive heart failure, and arrhythmias. The specificity was generally >85% for each condition.

A structured risk factor questionnaire was administered at baseline, including questions about smoking, alcohol consumption, diet, physical activity, and injuries. With regard to head injury, patients were asked whether they had ever had a head injury that resulted in loss of consciousness or amnesia. If the answer to this question was yes, they were asked whether they were hospitalized for that injury, when the injury occurred, and how long they were unconscious. With regard to smoking, patients were asked whether they had ever smoked at least one cigarette, one cigar, or one pipe-full per day for at least 1 year. If the answer to any one of these questions was yes, patients were asked whether they still smoked, how old they were when they began smoking, how old they were when they stopped smoking, and how many cigarettes, cigars, or pipe-fulls on average they smoked per day. From this information, average tobacco use over a lifetime was calculated. A similar set of questions was used for alcohol and coffee consumption. For alcohol consumption, patients were asked whether they had ever drunk at least one beer, one glass of wine, or one drink of hard liquor or spirits per week for at least 6 months, and how many 12-ounce bottles or cans of beer, 4-ounce glasses of wine, and 1-ounce (a jigger) servings of hard liquor or spirits they drank on average per week. For coffee consumption, patients were asked whether they had ever drunk at least one cup of coffee per day for at least 6 months and how many cups of coffee on average they drank per day.

The neuropsychological battery consisted of tests of

verbal and nonverbal memory, orientation, visuospatial ability, language, and abstract reasoning.[37] Neuropsychological test scores were evaluated by using a fixed paradigm,[37] and dementia was diagnosed based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, revised third edition (DSM III-R).[38]

Data Analysis

We decided a priori to study the association of head injury, smoking, hypertension, and diabetes mellitus with incident dementia in PD. The association of head injury with incident dementia was analyzed by assessing the risk of those who reported head injury with loss of consciousness in relation to those who did not. Those who reported head injury with loss of consciousness for less than 5 minutes or greater than or equal to 5 minutes were also analyzed separately. Hypertension and diabetes mellitus were analyzed by comparing those who reported the condition to those who did not. Because only four patients with hypertension and one patient with diabetes mellitus were not being treated, these patients were not analyzed separately.

Smoking was analyzed by comparing ever smokers, past smokers, and current smokers to nonsmokers. The number of pack-years was calculated by dividing the average number of cigarettes per day by 20 and multiplying this value by the number of years of smoking. We did not perform separate analyses for cigar- or pipe-smoking, because these were relatively infrequent exposures; among patients who did not smoke cigarettes, two smoked cigar, three smoked pipe, and two smoked both. However, we included cigar or pipe smokers along with cigarette smokers in the comparison between smokers and nonsmokers. The amount of alcohol consumed was calculated as the number of drinks/week by summing up the average number of 12-ounce bottles or cans of beer/week, 4-ounce glasses of wine/week, and 1-ounce (a jigger) servings of hard liquor or spirits/week. The amount of coffee consumed was expressed as the average number of cups/day.

Baseline characteristics of patients with and without incident dementia were compared by using Student's *t* tests for continuous variables and χ^2 tests for categorical variables. The association of head injury, smoking, hypertension, and diabetes mellitus (according to information obtained at baseline) with incident dementia was studied by using Cox proportional hazards models. The proportional hazards assumption of the Cox models was checked by examining the Martingale residuals.[39] Duration of follow-up from baseline until diagnosis of dementia or until the last visit for those patients who did not become demented was used as the timing variable in the Cox model. Dose-response effects were analyzed by calculating risk ratios for values above and below the median. All analyses controlled for age at baseline, gender, years of education, duration of PD, and the total motor score (part III) of the UPDRS at baseline.

In supplementary analyses, to examine the possibility of confounding by vascular factors, we adjusted for the occurrence of signs or symptoms of stroke during the follow-up period and for the occurrence of any of the following cardiovascular conditions before or during the follow-up period in the Cox model: hypertension, diabetes mellitus, myocardial infarction, congestive heart failure, valvular heart disease, angina, atrial fibrillation, and other cardiac arrhythmias. We also explored the association of addictive behaviors other than smoking, ie, alcohol and coffee consumption, with incident dementia in PD.

RESULTS

Of 180 patients, 52 (29%) became demented during a mean follow-up period of 3.6 ± 2.2 years (range, 0.5 to 8 years). Baseline demographic and clinical characteristics of the cohort are summarized in Table 1. Patients who subsequently became demented were significantly older, less educated, and had more severe motor signs at baseline than those who did not become demented.

Head injury with loss of consciousness, hypertension, and diabetes mellitus were not significantly associated with incident dementia in the Cox model controlling for age at baseline, gender, years of education, duration of PD, and total UPDRS motor score at baseline (Table 2). Patients who reported having ever smoked cigarettes, cigars, or pipes showed an increased risk of incident dementia compared with nonsmokers (RR, 2.0; 95% confidence interval [CI], 1.0–3.9; $P = 0.05$). Current smoking was significantly associated with incident dementia (RR, 4.5; 95% CI, 1.2–16.4; $P = 0.02$), whereas past smoking approached significance (RR, 1.9; 95% CI, 0.9–3.7; $P = 0.07$). To examine a dose-response effect, we dichotomized the number of pack-years and duration of smoking at the median. The median number of pack-years was 23 (range, 0.05–149 pack-years), and the median duration of smoking was 30 years (range, 1–74 years). No increasing risk with increasing number of pack-years or duration of smoking was observed (Table 2).

The mesolimbic dopaminergic system has been implicated in the addiction to nicotine.[40] To examine the possibility that the association between smoking and incident dementia was related to preservation of smoking

TABLE 1. *Baseline demographic and clinical characteristics of Parkinson's disease (PD) patients who did and did not become demented*

Variable	Incident dementia n = 52 mean (S.D.)	No incident dementia n = 128 mean (S.D.)	Total n = 180 mean (S.D.)
Age (yr)	74.6 (8.2)	69.5 (10.7)*	71.0 (10.3)
Education (yr)	9.4 (4.6)	11.8 (4.7)*	11.1 (4.8)
Gender (% M)	55.8	42.2	46.1
Ethnicity (% white non-Hispanic)	55.8	54.7	55.0
Primary language (% English)[b]	52.9	65.4	61.8
Duration of PD (yr)	7.3 (5.8)	5.9 (7.2)	6.3 (6.9)
Total UPDRS motor score[a] (range 0–100)[b]	32.0 (13.6)	22.2 (11.4)*	25.0 (12.8)
Total 17-item HDRS score[a] (range 0–53)[b]	6.8 (5.6)	5.8 (5.0)	6.1 (5.1)
Use of dopaminergic agents (%)[c]	76.9	75.8	76.1
Use of anticholinergics (%)[b]	17.6	15.2	15.9
Levodopa dosage (mg/day)[b]	326.7 (325.3)	364.2 (373.6)	354.1 (360.6)
Estrogen replacement therapy (%)[b]	4.3	17.8	14.6

*$P < 0.05$.

[a]HDRS, Hamilton Depression Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

[b]Total n: 178 for language, 177 for UPDRS score, 154 for HDRS score, 176 for use of anticholinergics, 159 for levodopa dosage, and 96 for estrogen replacement therapy.

[c]Includes levodopa and dopaminergic agonists.

behavior, we analyzed the length of time between smoking cessation and PD onset. The rationale for using PD onset as a reference was that, at this point, patients would have approximately the same amount of dopaminergic deficiency, based on the estimation that 70% of the nigrostriatal system is damaged when parkinsonian symptoms appear.[41] For past smokers, we calculated the age at which the patient stopped smoking minus the age at onset of PD. For current smokers, because we did not have information about smoking after baseline evaluation, we subtracted age at onset of PD from age at baseline. Median length of time between smoking cessation and PD onset was 8 years before PD onset (range, 62 years before PD onset to 27 years after PD onset). When we analyzed patients who stopped smoking ≥ 8 years before PD onset and patients who stopped smoking < 8 years before PD onset (including patients who stopped smoking after PD onset and patients who had not stopped smoking at the time of baseline evaluation) compared with nonsmokers, we observed an increasing risk of in-

TABLE 2. *Association of head injury, smoking, hypertension, and diabetes mellitus with incident dementia in Parkinson's disease (PD)**

Exposure	Frequency within incident dementia (%)[a]	Frequency within no incident dementia (%)[a]	Risk ratio	95% confidence interval	*P*
Head injury with loss of consciousness					
Yes vs. no	8/51 (15.7)	15/127 (11.8)	0.9	0.4–2.2	0.9
<5 min. vs. no	2/50 (4.0)	6/127 (4.7)	1.0	0.2–4.4	1.0
≥5 min. vs. no	5/50 (10.0)	9/127 (7.1)	0.8	0.2–2.4	0.6
Hypertension					
Yes vs. no	16/52 (30.8)	52/128 (40.6)	0.7	0.4–1.4	0.3
Diabetes mellitus					
Yes vs. no	4/52 (7.7)	12/128 (9.4)	0.8	0.3–2.3	0.7
Smoking					
Ever vs. nonsmokers	29/50 (58.0)	50/127 (39.4)	2.0	1.0–3.9	0.05
Past vs. nonsmokers	25/50 (50.0)	44/127 (34.6)	1.9	0.9–3.7	0.07
Current vs. nonsmokers	4/50 (8.0)	6/127 (4.7)	4.5	1.2–16.4	0.02
≤23 pack/yr vs. nonsmokers	11/46 (23.9)	24/122 (19.7)	2.4	1.1–5.3	0.04
>23 pack/yr vs. nonsmokers	14/46 (30.4)	21/122 (17.2)	1.5	0.7–3.3	0.3
Duration ≤30 yr vs. nonsmokers	11/47 (23.4)	27/126 (21.4)	1.9	0.9–4.3	0.1
Duration >30 yr vs. nonsmokers	15/47 (31.9)	22/126 (17.5)	1.7	0.8–3.9	0.2
Cessation ≥8 yr before PD onset vs. nonsmokers	12/49 (24.5)	26/126 (20.6)	1.5	0.7–3.6	0.3
Cessation <8 yr before PD onset vs. nonsmokers[b]	16/49 (32.7)	23/126 (18.3)	2.3	1.1–4.9	0.03

*Risk ratios derived from Cox proportional hazards models controlling for age at baseline, gender, years of education, duration of PD, and total Unified Parkinson's Disease Rating Scale motor score.

[a]The sum of the denominators for some risk factors does not equal 180 because of missing data.

[b]Also includes patients who stopped smoking after PD onset and current smokers at baseline.

cident dementia with later cessation of smoking (Table 2 and Fig. 1).

To examine the possibility of confounding by vascular factors in the association of smoking and incident dementia, we first repeated the analysis adjusting for the occurrence of signs or symptoms of stroke during the follow-up period. Second, we repeated the analysis adjusting for a dichotomous variable taking into consideration the occurrence of cardiovascular conditions before or during the follow-up period. In both cases, the results were not substantially different. A subsample of 133 patients (74%) had *APOE4* genotype information; 31 had at least 1 *APOE-ε4* allele and 102 had no *APOE-ε4* allele. When the presence of at least 1 *APOE-ε4* allele was included in a Cox model controlling for age at baseline, gender, years of education, duration of PD, and total UPDRS motor score at baseline, it was not significantly associated with incident dementia (RR, 0.7; 95% CI, 0.2–1.8; $P = 0.4$). Therefore, we did not further explore the possibility of confounding by *APOE4* genotype in the analyses.

Because of the association between smoking and incident dementia, in a secondary analysis, we explored the association of other addictive behaviors with incident dementia in PD. No statistically significant association was found between alcohol or coffee consumption (at least one drink/week and one cup of coffee/day, respectively) and incident dementia, when comparing ever, past, or current users to nonusers (Table 3). Among those who drank alcohol, the median amount consumed was six drinks/week (range, 1 to 61 drinks/week). For coffee consumption, the median amount was two cups/day (range, 1 to 15 cups/day).

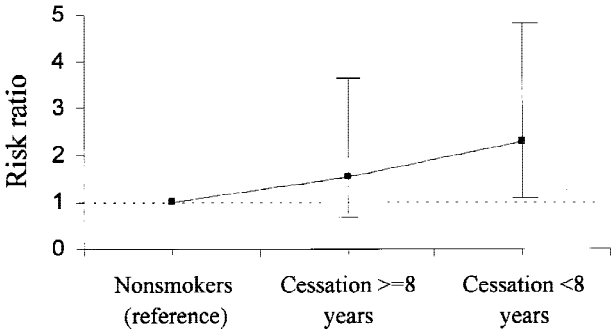

FIG. 1. Dose-response effect for smoking cessation in relation to Parkinson disease (PD) onset (P for linear trend: 0.03). Cessation $\geq$ 8 years includes those who stopped smoking 8 or more years before PD onset. Cessation < 8 years includes those who stopped smoking less than 8 years before PD onset, those who stopped smoking after PD onset, and current smokers at baseline evaluation. Risk ratios and 95% confidence intervals were calculated by comparing both groups to nonsmokers (reference group) in a Cox proportional hazards model controlling for age at baseline, gender, years of education, duration of PD, and total Unified Parkinson Disease Rating Scale (UPDRS) motor score at baseline.

DISCUSSION

In this study, PD patients who reported having ever smoked had twice the risk of developing dementia compared with nonsmokers, whereas current smokers had an even higher relative risk. No statistically significant association was found between head injury, hypertension, and diabetes mellitus and incident dementia in PD. Some baseline differences between patients with and without incident dementia in Table 1 are noteworthy, although not statistically significant. Male gender was present in 55.8% of incident dementia cases and in 42.2% of no incident dementia cases. Consistent with a previous study,[29] estrogen replacement therapy was more frequent in the group that did not develop incident dementia. The higher frequency of English-speaking patients among patients without incident dementia is probably related to their significantly higher education.

The association of smoking and AD is not consistent across studies. An inverse association was first observed in case control studies, with a trend for decreasing risk with increasing tobacco consumption.[42,43] More recently, some but not all prospective cohort studies have found that smoking increased rather than decreased the risk of AD.[18–20,44,45] On the other hand, an inverse association of smoking and PD has been consistently demonstrated in many studies.[46,47] Nevertheless, it remains controversial whether this inverse association is causal, suggesting a protective effect of smoking, or related to loss of addictive drive or personality changes in the preclinical stages of PD.[48–50] Few previous studies have examined the association of smoking with dementia in PD. Among four cardiovascular risk factors (hypertension, diabetes mellitus, smoking, and coronary heart disease) examined in a case control study, hypertension was significantly associated with dementia in PD. The frequency of smoking was 38% among demented and 27% among nondemented PD patients, but there was no significant difference between the groups.[8] In two other case control studies, including our own using a smaller and separate sample, smoking was not significantly associated with dementia in PD, although it was more frequently observed in demented compared with nondemented PD patients.[6,9] In the only other longitudinal study evaluating the association of smoking with incident dementia in PD, Ebmeier and colleagues[51] reported a fourfold significantly increased risk for dementia in PD during a 3.5-year follow-up period in those having a history of smoking.

TABLE 3. *Association of alcohol and coffee consumption with incident dementia in Parkinson's disease**

Exposure	Frequency within incident dementia (%)[a]	Frequency within no incident dementia (%)[a]	Risk ratio	95% confidence interval	*P*
Alcohol					
Ever vs. nonusers	21/50 (42.0)	52/126 (41.3)	1.1	0.6–2.2	0.8
Past vs. nonusers	17/50 (34.0)	27/126 (21.4)	1.3	0.6–2.7	0.5
Current vs. nonusers	4/50 (8.0)	25/126 (19.8)	0.8	0.3–2.3	0.6
Coffee					
Ever vs. nonusers	38/50 (76.0)	103/126 (81.7)	0.9	0.5–1.8	0.7
Past vs. nonusers	15/50 (30.0)	28/126 (22.2)	1.4	0.6–3.0	0.4
Current vs. nonusers	23/50 (46.0)	75/126 (59.5)	0.7	0.3–1.5	0.4

*Risk ratios derived from Cox proportional hazards models controlling for age at baseline, gender, years of education, duration of PD, and total Unified Parkinson's Disease Rating Scale motor score.

[a]The sum of the denominators does not equal 180 because of missing data.

Like the inverse association of smoking and PD, the direct association of smoking and dementia in PD could be considered as either causal or related to addictive behavior. Currently, no biological explanation for a causal relationship between smoking and PD dementia seems evident. Greater depletion of cholinergic cells in the nucleus basalis of Meynert has been observed in PD with dementia compared with PD without dementia.[11] However, the up-regulation of central nicotinic acetylcholine receptors by nicotine[52] and the beneficial effects of nicotine on cognitive function[53] would not be consistent with a causal relationship between smoking and PD dementia through mechanisms involving the cholinergic system. Although we controlled for the occurrence of stroke and cardiovascular conditions in our analysis, the possibility of a vascular mechanism mediating this association cannot be completely ruled out because of the lack of neuroimaging examinations in our patients.

The mesolimbic dopaminergic system has an important role in the brain reward mechanism operant in smoking and other addictive disorders,[54,55] and its early involvement may account for a loss of addictive drive in PD patients before the motor manifestations of the disease.[41] The finding of an increasing risk of dementia with later cessation of smoking relative to PD onset suggests that the association of smoking and PD dementia may reflect preservation of addictive behavior. Noradrenergic deficiency due to neuronal loss in the locus ceruleus occurs to a greater extent in PD with dementia compared with PD without dementia.[56,57] Interactions between noradrenaline and dopamine have been suggested to affect activated and stress-induced behaviors, including reward processes, in such a way that impairment of noradrenergic function would counteract or normalize the effects of decreased dopamine function.[58,59] Thus, more widespread subcortical pathology with additional nondopaminergic neurotransmitter deficiency in PD patients at higher risk of developing dementia could lead to continued addictive behavior. That we did not find a similar relationship between alcohol and coffee consumption and PD dementia does not support this hypothesis. However, differences in addictive drive might have been more difficult to discern in these analyses, because 78% of those who reported coffee consumption consumed $\leq$ 2 cups of coffee/day and 66% of those who reported alcohol consumption consumed $\leq$7 drinks/week. When we defined coffee and alcohol use by the upper quartile of consumption ($\geq$3 cups of coffee/day and $\geq$12 drinks/week, respectively), the results were still nonsignificant, but the proportion of coffee and alcohol users further limited the statistical power of these analyses (data not shown).

The prospective cohort design of our study avoided some of the problems associated with case control studies such as recall bias, the use of surrogate respondents for demented patients, and the effect of dementia itself on risk factors. However, our study has limitations. This is a prevalent PD cohort with mean disease duration at baseline evaluation of 6.3 ± 6.9 years (median, 4.2 years). As is true for other cohorts of prevalent nondemented PD cases,[4,5] patients with more rapidly progressive disease or patients more likely to become demented may have been excluded. Information regarding hypertension and diabetes mellitus was obtained from the patient and the caregiver at baseline. Although we may have missed cases of undiagnosed hypertension and diabetes mellitus, there is no reason to suppose that these cases would be differentially represented in the groups with and without incident dementia. We based our calculation of pack-years on the average number of cigarettes smoked per day, rather than on a weighted average taking into account changes in the amount smoked per day over time. A calculated lifetime dose would be more appropriate, and this may have obscured a dose-response

effect in our analysis. Because our study tested associations of multiple risk factors with incident dementia in PD, there is a possibility of a type I error. Therefore, this study should be considered exploratory. In addition, the twofold risk of smoking for incident dementia in PD should be interpreted cautiously, as it was of marginal statistical significance and the lower limit of the 95% confidence interval approached 1. On the other hand, compared with epidemiologic studies of AD, the size of our cohort was relatively small, which limited our power for detecting statistically significant associations. Our sample size prevented stratification by *APOE4* genotype; the number of patients with at least 1 *APOE-ε4* allele was too small to observe effect modification by *APOE4*, as has been shown in the association of smoking[18,20] and head injury[15,17] with AD.

In conclusion, among the four risk factors examined (head injury, smoking, hypertension, and diabetes mellitus), our results suggest that only smoking is associated with incident dementia in PD. Although an inverse association between smoking and PD has been reported in several studies, our study showed a positive association between smoking and dementia in the setting of PD. Overall, our findings, together with the lack of association of *APOE4* genotype and dementia in PD reported in previous studies,[27,28] do not support the hypothesis of a common etiologic basis for PD dementia and AD. However, because the pathological substrate of dementia in PD may be heterogeneous,[11,12] these epidemiologic findings are consistent with the possibility that some PD dementia patients have concomitant AD. The association of smoking with incident dementia in PD needs to be further studied.

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