

Smoking and Parkinson's disease in twins

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Abstract—Objective: To test the hypothesis that cigarette smoking protects against the development of PD. **Background:** Smoking has been inversely associated with PD in many studies, but whether this reflects a biologic effect on the underlying disease process or merely confounding or selection bias remains uncertain. **Methods:** The authors compared smoking histories in male twin pairs identified from the National Academy of Sciences–National Research Council World War II Veteran Twins Cohort. The amount of cigarettes smoked (in pack-years) was collected until the time of PD onset in the affected twin or until the time of death for the unaffected twin, whichever came first. Differences in pack-years smoked until PD onset and until 10 and 20 years before onset were compared using paired *t*-tests. Comparisons were made overall and stratified by zygosity and concordance for PD. To assess the role of shared environment, correlation for smoking behaviors was compared between pairs concordant and discordant for PD. **Results:** Detailed smoking histories were available for 113 twin pairs in which at least one twin had PD (discordant pairs: 43 monozygotic [MZ], 50 dizygotic [DZ]; concordant pairs: 10 MZ, 10 DZ). Within-pair correlation for ever smoking was high in MZ pairs ($\phi = 0.47$, $p = 0.001$) but not in DZ pairs ($\phi = 0.007$, $p = 0.96$). In 33 discordant MZ pairs and 39 discordant DZ pairs in which at least one twin had smoked, the twins without PD smoked more than their brothers smoked (32.5 vs 22.7 pack-years, $p = 0.026$). This was more marked in the MZ pairs (37.1 vs 25.3 pack-years, $p = 0.077$) than in the DZ pairs (28.6 vs 20.5 pack-years, $p = 0.17$). A similar relationship was seen when smoking dose was calculated only until 10 years before PD onset, suggesting that the lower dose of smoking in the twin with PD was not the result of early, undiagnosed disease. **Conclusion:** Within twin pairs, risk of PD is inversely correlated with the dose (in pack-years) of cigarette smoking. This effect is most pronounced in MZ twins, despite the high correlation for smoking. Because MZ twins are genetically identical and are similar behaviorally, this difference is unlikely to result from either genetic factors or environmental confounders. These results are compatible with a true biologic protective effect of cigarette smoking.

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Although the biologic basis of the observation that cigarette smoking protects against PD is controversial, this association has been found in diverse populations in studies spanning more than 30 years.^{1–13} Overall, risk of PD in persons who ever smoked has been found to be about half that of lifelong nonsmokers. Biologic hypotheses to explain this have focused largely on nicotine, including induction of detoxifying enzymes, inhibition of bioactivating enzymes, and trophic factor stimulation, but none have been proven.^{14–21} Others have argued that nonsmoking is one aspect of a “pre-parkinsonian personality,” which may be inherited.^{9,22–24} Increasingly, specific genetic factors, for example, certain alleles encoding enzymes related to the dopaminergic system, have been associated with smoking behaviors, lending some biologic plausibility to the pre-parkinsonian personality hypothesis.^{14,25–28} However, separating an inherent genetic predisposition to both PD and smoking from any independent action of nicotine or another component of cigarette smoke has remained an elusive scientific task.

This investigation circumvents some of the problems inherent in previous studies testing the hypothesis that cigarette smoking protects against PD by

taking the novel approach of determining smoking behaviors in twins discordant for PD. Because twins are genetically identical (if monozygotic [MZ]) or similar (if dizygotic [DZ]), the potential confounding effect of genetic factors is controlled.

Methods. *Subjects.* Twins with PD were identified from among members of the National Academy of Sciences–National Research Council (NAS-NRC) World War II Veteran Twins Registry²⁹ using a multistage screening method with confirmation by neurologic examination. A detailed description of case ascertainment has been published previously.³⁰ Subjects from this cohort were included in the current study if they met the following criteria: 1) PD had been diagnosed in the subject or his twin brother; and 2) cigarette smoking histories were available for both members of the twin pair. All persons who were identified by a tiered telephone interview screening process as possibly having PD, and their twins, were evaluated and examined in person whenever possible.

Diagnostic criteria. Diagnostic criteria from the Core Assessment Program for Intracerebral Transplantations³¹ were used. “Probable PD” was defined as 1) the presence of at least two of the following signs, at least one of which must be either resting tremor or bradykinesia: resting

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tremor, cogwheel rigidity, bradykinesia, and postural reflex impairment; 2) no other cause of parkinsonism; 3) no signs of more extensive neurodegeneration indicating atypical parkinsonism; and 4) a clearcut response to L-dopa, if treated. "Possible PD" was defined in one of the following ways: a) meets criteria 2 through 4 just listed, but neither bradykinesia nor resting tremor is present; b) meets criteria 2 through 4 just listed, but only resting tremor is present; c) meets criteria 1 through 3, but response to L-dopa is unknown; or d) meets all of criteria 1 through 4 but also has another clinical symptom or sign sometimes found in PD (e.g., prominent dementia, severe dysautonomia).

Final diagnosis. All in-person evaluations were reviewed independently by a second neurologist blinded to 1) zygosity, 2) disease status of the twin brother, and 3) the in-person examiner's diagnosis. If the examining and reviewing neurologists agreed with the diagnosis based on direct examination, this diagnosis was accepted. When disagreement occurred, final diagnosis was established by consensus of two blinded neurologists who reviewed all available information. For twins who were dead or who refused in-person examination, diagnostic criteria were applied using all available information (including medical records, proxy interviews, death certificates).

Zygosity. Zygosity was determined by multiple polymerase chain reactions when possible³² and by standard questions^{33,34} when DNA was not available for both twins.

Smoking history. Trained interviewers collected life-long histories of cigarette smoking by telephone using a structured interview. Smoking history was obtained as part of a larger lifetime risk-factor interview, and subjects were not informed of any specific study hypotheses. A different interviewer questioned each twin in a pair, and as much as possible, interviewers were blinded to disease status. A brief dementia screen, the modified Telephone Interview for Cognitive Status (TICS-m),³⁵ was administered before obtaining the cigarette smoking history; subjects scoring below an education-adjusted cutoff score were classified as demented. Proxy historians were identified for dead and demented subjects. Total pack-years of cigarette smoking (packs per day times years smoked) were computed for each subject.

Analyses. Cigarette smoking before the index date was compared within twin pairs. The index date was defined as 1) for discordant pairs, the year of diagnosis in the twin with PD or the year of death in the twin without PD, whichever came first; and 2) for concordant pairs, the year of PD diagnosis in the twin first diagnosed. Twin pairs discordant and concordant for PD were analyzed separately. The hypothesis that smoking is inversely associated with PD was tested within discordant twin pairs by comparing the following: 1) "ever smoking" (defined as a lifetime total of 100 or more cigarettes smoked before index date), 2) regular smoking (defined as more than one cigarette daily for 3 months or more), and 3) number of pack-years smoked. Within twin pairs concordant for PD, the hypothesis that ever smoking, regular smoking, or greater number of pack-years smoked is associated with a later disease onset age was tested. Analyses were first performed in strata defined by respondent type (proxy, non-proxy) and pooled only if results were similar.³⁶

Because smoking behavior may have changed as the

result of early, undiagnosed PD, analyses also were performed for the periods 10 years and 20 years before the index date. Analyses of "total" tobacco exposure, including cigarettes, cigars, pipes, and chewing tobacco, also were performed for each of these strata. Within-pair correlations were assessed by the phi coefficient for nominal data, categorical associations by McNemar's test, and continuous associations by paired *t*-tests. Analyses were performed using SPSS, Version 8.0 for Windows (SPSS Inc., Chicago, IL).

Results. Subjects. In 1992, at the time of initiating the telephone screen, the NAS-NRC database contained 19,842 twins who were believed to be alive (zygosity by self-report: 37.3% MZ, 47.5% DZ, and 15.2% unknown). Of this group, we were able to carry out screening interviews in 14,436 living twins. Interviews were carried out using proxy informants for an additional 2,689 twins. On completion of the interviews and examinations of probable cases, PD was diagnosed in 193 twins who were members of 172 pairs.³⁰ Fifty of these pairs were excluded from the current study because of incomplete smoking histories in 1 of the twins, and 9 others were excluded because of incomplete diagnostic information. Of the remaining 113 pairs, 93 were discordant (43 MZ, 50 DZ) and 20 were concordant (10 MZ, 10 DZ) for PD. The mean age at diagnosis was similar in twins from discordant and concordant pairs (63.9 years and 64.0 years, respectively). Proxy respondents provided the smoking history for 81 individuals (36%). Twins with PD were significantly more likely than the unaffected twins to have a proxy respondent (44% vs 25%). Proxy respondent proportions did not differ significantly by zygosity.

Smoking behavior. In the 226 individual twins, 63% of twins with PD and 69% without PD had ever smoked cigarettes. Both twins in MZ pairs discordant for PD were likely to have similar smoking behavior, but this was not true for twins in DZ pairs (table 1). In pairwise analyses, PD risk was not significantly different in ever cigarette smokers or regular cigarette smokers overall or when stratified by zygosity or informant type. However, in discordant pairs in which at least one twin smoked, the dose of cigarettes smoked was significantly greater in the twin without PD (table 2). Overall, the twin without PD had smoked an average of 9.7 more pack-years than his twin with PD, before the index date. Significant differences persisted when dose was calculated until 10 years or 20 years before index date. When pairs were stratified by zygosity, controls tended to smoke more and longer than their affected twin, but differences were not significant, possibly because of the smaller number of subjects within strata. Pack-year differences were greater within MZ pairs than within DZ pairs, and strata-specific differences persisted when dose was calculated until 10 or 20 years before index date. Results were similar when analyses were limited to those discordant pairs in which both twins were alive at the time of PD diagnosis in the affected twin (64 pairs) (table 3).

Risk differences were unaffected by the inclusion of non-cigarette tobacco sources in each of these analyses (data not shown).

In concordant pairs (table 4), cumulative cigarette smoking dose also tended to be less in the twin with earlier

Table 1 Ever and regular smoking in twin pairs with PD in at least one twin

Smoking history	All pairs		Pairs discordant for PD		Pairs concordant for PD	
	MZ, n = 53	DZ, n = 60	MZ, n = 43	DZ, n = 50	MZ, n = 10	DZ, n = 10
Ever smoked*						
Both twins	31	21	25	21	6	0
Only twin with PD (or first onset twin if concordant)	4	12	4	9	0	3
Only twin without PD (or second onset if concordant)	8	17	6	12	2	5
Neither twin	10	10	8	8	2	2
Correlation for smoking within pairs by zygosity, phi	0.47, <i>p</i> = 0.001	0.007, <i>p</i> = 0.96	0.45, <i>p</i> = 0.003	0.10, <i>p</i> = 0.47	0.61, <i>p</i> = 0.053	-0.66, <i>p</i> = 0.038
Correlation for smoking within pairs overall, phi	0.22, <i>p</i> = 0.019		0.26, <i>p</i> = 0.012		0.032, <i>p</i> = 0.89	
Risk for smokers, OR (95% CI)	0.50 (0.19–1.2)	0.71 (0.46–1.1)	0.67 (0.34–1.2)	0.75 (0.51–1.1)	0 (N/A)	0.60 (0.25–1.3)
Risk, any zygosity, OR (95% CI)	0.64 (0.39–1.05)		0.72 (0.44–1.06)		0.43 (0.12–1.2)	
Smoked regularly*						
Both twins	29	19	23	19	6	0
Only twin with PD (or first onset twin if concordant)	4	12	5	9	0	3
Only twin without PD (or second onset if concordant)	8	16	6	11	2	5
Neither twin	10	12	8	10	2	2
Correlation for smoking within pairs by zygosity, phi	0.43, <i>p</i> = 0.002	0.42, <i>p</i> = 0.75	0.40, <i>p</i> = 0.009	0.19, <i>p</i> = 0.40	0.61, <i>p</i> = 0.053	-0.66, <i>p</i> = 0.038
Correlation for smoking within pairs overall, phi	0.22, <i>p</i> = 0.018		0.28, <i>p</i> = 0.028		0.032, <i>p</i> = 0.89	
Risk for smokers, OR (95% CI)	0.50 (0.19–1.2)	0.75 (0.52–1.1)	0.83 (0.57–1.2)	0.82 (0.60–1.1)	0 (N/A)	0.60 (0.25–1.3)
Risk, any zygosity, OR (95% CI)	0.67 (0.42–1.1)		0.82 (0.63–1.1)		0.43 (0.12–1.2)	

* McNemar tests for ever or regular smoking by zygosity and overall are all nonsignificant.

DZ = dizygotic; MZ = monozygotic; N/A = not applicable.

disease onset, although the number of pairs is small and results are not significant. Whether dose was truncated at PD onset in the first affected twin, or 10 or 20 years before PD onset, the twin with earlier onset tended to smoke fewer pack-years than his twin. Similar trends also were observed in all strata for smoking duration and with the inclusion of non-cigarette tobacco sources (data not shown).

Discussion. An inverse association between cigarette smoking and PD has been reported in more than a dozen case-control studies¹⁻¹² and in several prospective investigations.^{13,37-39} The risk of PD in smokers appears to be about one-half that of non-smokers.⁴⁰ Although this association has turned up repeatedly in epidemiologic studies, a clearcut biologic basis for this phenomenon has yet to be identified. This is important because it could help to identify the cause of the disease and strategies for prevention. One hypothesis is that smoking protects against the development of PD because of its effect on the enzyme monoamine oxidase (MAO). Cigarette smoke reduces MAO A and MAO B activity in

animal and human brain.^{14,41} MAO B activates the parkinsonism-inducing neurotoxin MPTP, and MAO B inhibitors may offer neuroprotection in PD.^{42,43} Furthermore, cigarette smoke reduces human striatal dopamine turnover⁴⁴ and reduces levels of putative endogenous neurotoxins in rat brain.²¹

A second hypothesis is that nicotine itself is neuroprotective. Several protective actions of nicotine have been described in animal models, including protection against age,¹⁷ transection,^{15,16} and MPTP-induced dopaminergic neuronal toxicity.^{18,20,45} Nicotine also has antioxidant properties⁴⁶ and has been shown to increase levels of trophic factors in rodent striatum.^{19,20,47}

Despite the consistency of the epidemiologic observations and the biologic plausibility of a protective effect of cigarette smoking on the development of PD, a cause-and-effect relationship is not universally accepted. First, not all studies have observed an inverse association between smoking and PD.^{8,48-52} Second, some investigators argue that the inverse association could be an “effect-cause” phenomenon if

Table 2 Mean pack-years and duration of cigarette smoking within twin pairs discordant for PD in which at least one twin smoked regularly

Endpoint for pack-years calculation	PD twin	Control twin	Excess smoked by control twin (SE)	<i>p</i> Value (two-tailed, paired <i>t</i> -test)
PD diagnosis				
MZ pairs, n = 33				
Pack-years	25.3	37.1	11.7 (6.4)	0.077
Years smoked	22.4	27.5	5.1 (4.2)	0.24
DZ pairs, n = 39				
Pack-years	20.5	28.6	8.1 (5.8)	0.17
Years smoked	19.5	22.1	2.6 (3.9)	0.50
All pairs, n = 72				
Pack-years	22.7	32.5	9.7 (4.3)	0.026
Years smoked	20.8	24.5	3.7 (2.8)	0.19
10 y before PD				
MZ pairs				
Pack-years	23.2	32.9	9.7 (5.7)	0.10
Years smoked	20.6	24.4	3.8 (3.6)	0.30
DZ pairs				
Pack-years	18.4	25.3	6.9 (4.9)	0.16
Years smoked	17.8	19.6	1.8 (3.4)	0.60
All pairs				
Pack-years	20.6	28.8	8.2 (3.7)	0.030
Years smoked	19.1	21.8	2.7 (2.4)	0.27
20 y before PD				
MZ pairs				
Pack-years	19.3	25.4	6.2 (4.4)	0.17
DZ pairs				
Pack-years	13.9	19.7	5.7 (3.5)	0.11
All pairs				
Pack-years	16.5	22.4	5.9 (2.8)	0.035

DZ = dizygotic; MZ = monozygotic.

case subjects have a higher rate of smoking cessation before their diagnosis, or it may be caused by biased ascertainment if case subjects have greater smoking-related mortality than control smokers.⁵³⁻⁵⁵ Third, the apparent effect of nicotine instead may represent confounding by another substance often associated with nicotine. This last possibility is unlikely, however, because several studies have found independent protective associations between smoking, caffeine, and ethanol and PD risk.^{37,38,56,57}

Finally, rather than indicating a causal relationship, decreased smoking in PD could result from confounding by disease-related factors. This last possibility is both plausible and hard to assess. For example, patients with PD often are described as having a conservative, restrained personality manifesting many years before their diagnosis.^{4,23,24,58,59} This personality profile, in turn, could reflect a common underlying genetic or metabolic factor. Indirect

support for this is provided by the observations that both smoking behavior and personality are associated with dopaminergic functions.^{14,25-28} Interestingly, twin studies also support a genetic basis for some smoking behaviors. Concordance for smoking initiation, amount smoked, and the ability to quit smoking is greater in MZ than in DZ twin pairs.⁶⁰⁻⁶⁵ Similarly, MZ twins are concordant more often than DZ twins for many personality traits. If some genetic factor predisposes both to smoking and to PD, then the association between cigarette smoking and PD may reflect confounding by a shared genetic substrate. If this is true, the inverse association between PD and cigarette smoking would not be expected to be found in paired analyses of MZ twin pairs, in whom all nuclear-encoded genes are identical, and would be less likely to be observed in DZ pairs, who are more genetically similar to their twin brothers, on average, than population controls. Conversely, if

Table 3 Mean pack-years of cigarette smoking in twin pairs discordant for PD, in which at least one twin smoked regularly and the control twin was alive at the time of his twin's diagnosis

Endpoint for pack-years calculation	PD twin	Control twin	Excess smoked by control twin (SE)	<i>p</i> Value (two-tailed, paired <i>t</i> -test)
PD diagnosis				
MZ pairs, n = 29				
Pack-years	26.9	39.6	12.7 (7.2)	0.091
DZ pairs, n = 35				
Pack-years	21.3	29.5	8.2 (6.4)	0.21
All pairs, n = 64				
Pack-years	23.8	34.1	10.2 (4.8)	0.037
10 y before PD				
MZ pairs, n = 29				
Pack-years	24.5	34.9	10.4 (6.5)	0.12
DZ pairs, n = 34				
Pack-years	18.9	26.0	7.1 (5.4)	0.20
All pairs, n = 63				
Pack-years	21.5	30.1	8.6 (4.1)	0.042
20 y before PD				
MZ pairs, n = 29				
Pack-years	20.5	26.8	6.3 (4.9)	0.21
DZ pairs, n = 33				
Pack-years	14.3	20.5	6.2 (3.9)	0.12
All pairs, n = 62				
Pack-years	17.2	23.4	6.3 (3.1)	0.046

DZ = dizygotic; MZ = monozygotic.

an inverse association is seen in twin pairs discordant for PD, the association is not likely to result from a confounding genetic factor.

In the current study, we observed a great degree of shared smoking behavior within twin pairs, particularly when categorical measurements (ever smoking, regular smoking) were used, in keeping with prior reports in twins. Smoking behaviors were highly correlated within twin pairs overall, and especially in MZ pairs, and smoking cigarettes per se was not associated with a decreased risk of PD. In contrast, when the actual cumulative amount of cigarettes smoked was measured (in pack-years), twins with PD smoked significantly less than their unaffected twin brothers. The magnitude of this dose difference was greatest in MZ twins despite the fact that the MZ twins also shared smoking behaviors to a greater degree. Because the nuclear DNA of MZ twins is identical, this inverse association of the amount of cigarettes smoked and PD cannot result from a genetically determined behavior encoded by nuclear DNA. Rather, the inverse association of smoking dose and PD can be attributed to environmental, and not genetic, causes with near certainty. The caveat to this is that mitochondrial DNA may differ between MZ twins. Our findings do not exclude the possibility that smoking behavior is in some way determined by mitochondrial DNA. However, we are

not aware of an association between genes residing on the mitochondrial genome and behavior.

A potential limitation of twin studies is the possibility that the great similarity in exposures in twins creates a situation of overmatching with consequent reduced power. Such a situation could produce a false-negative result. If only categorical measures of smoking had been used, we would have found such a result because these broad measures of smoking behavior were highly correlated within twin pairs. However, the more sensitive measure of smoking dose did distinguish between twins with PD and those without disease. This finding demonstrates the value of using the twin case-control method to distinguish genetic from environmental determinants. As reviewed earlier, an inverse association between cigarette smoking and PD has been reported in many prior studies, but the significance of this observation has been debated. This study is the only one to exclude a confounding effect of nuclear encoded genes.

We also took measures to deal with the effect-cause issue noted earlier. If individuals who are becoming ill quit smoking, then smoking will appear more frequent in twins without PD than in twins with PD. To control for this possible source of bias, we calculated cumulative smoking dose until disease onset and also until 10 years and 20 years before disease onset. A significant pack-year excess was

Table 4 Pack-years and duration of cigarette smoking within twin pairs concordant for PD in which at least one twin smoked regularly

Endpoint for pack-years calculation	Twin with earlier PD onset	Twin with later PD onset	Excess smoked by later PD onset twin (SE)
PD diagnosis			
MZ pairs, n = 7			
Pack-years	19.6	22.1	2.5 (5.7)
Years smoked	21.1	22.0	0.9 (9.0)
DZ pairs, n = 8			
Pack-years	3.5	5.0	1.5 (4.2)
Years smoked	4.2	6.0	1.8 (4.8)
All pairs, n = 15			
Pack-years	11.0	13.0	2.0 (3.4)
Years smoked	12.7	14.0	1.3 (4.9)
10 y before first PD			
MZ pairs			
Pack-years	14.5	17.1	2.6 (4.8)
Years smoked	18.4	19.7	1.3 (7.9)
DZ pairs			
Pack-years	3.4	5.0	1.6 (4.5)
Years smoked	3.7	6.0	2.3 (4.6)
All pairs			
Pack-years	8.5	10.6	2.1 (3.1)
Years smoked	11.1	12.9	1.8 (4.4)
20 y before first PD			
MZ pairs			
Pack-years	13.5	15.8	2.3 (3.9)
DZ pairs			
Pack-years	2.7	5.9	3.2 (4.7)
All pairs			
Pack-years	7.6	10.4	2.8 (3.0)

DZ = dizygotic; MZ = monozygotic.

found in (discordant) control twins using all three endpoints, suggesting that this finding did not result from bias caused by early disease features.

Whereas we believe that the results reported here are compelling regarding the inverse relationship between smoking and PD, notice that this study has several inherent weaknesses common to all epidemiologic investigations of this nature. However, we have taken steps to minimize these. Diagnostic misclassification of cases and controls always is a problem in studies of PD because the only diagnostic "gold standard" is postmortem examination. Although the diagnostic methods used in this study were thorough and the examiners highly experienced, some misclassification probably occurred. This diagnostic misclassification could result in either type I or type II error, but because atypical parkinsonism constitutes less than 10% of all cases of primary parkinsonism, it is unlikely to have a major statistical impact. Another problem with ret-

rospective case-control studies is recall bias. However, we believe that this is unlikely to have been a major factor in this study. Risk factors for PD are poorly characterized, and, therefore, study subjects have few systematic preconceived ideas regarding their disease etiology. Because smoking is a generally harmful behavior, biased recall would likely decrease the probability of observing an inverse association. Furthermore, recall bias is not a problem in concordant pairs, where both historians had disease. Proxy informants, who provided 36% of smoking histories, also may have misclassified exposures, but the magnitude of error for this type of data from proxies has been shown to be small.⁶⁶⁻⁶⁸ Moreover, excluding data derived from proxy informants did not alter our findings.

Whereas it could be argued that unrecognized features of PD could have been present more than 20 years before disease diagnosis (leading to reduced smoking in future cases), there are several reasons

to suggest that this was not the case. Although several retrospective studies of personality suggest that this may occur,^{23,69} recent evidence from PET studies suggests only a 7- to 10-year preclinical phase of dopaminergic neuronal pathology.⁷⁰ Furthermore, the relative magnitude of the observed smoking differences between case and control subjects was similar 10 and 20 years before disease and at disease onset, arguing against any major effect of early disease on reducing smoking behavior. Conversely, this study was not specifically designed to address possible bias because of increased mortality in smokers with PD, although a large prospective study argues against a major effect from differential mortality.^{13,71} If ascertainment was less complete in pairs with case subjects who smoked, bias could have resulted. To minimize this, we used a variety of case ascertainment methods, including Health Care Financing Administration billing codes, National Death Index, Veterans Administration records, and proxy interviews. That overall case prevalence in this cohort was similar to other thorough population-based surveys⁷²⁻⁷⁴ argues against any major ascertainment bias.

By controlling for genetic variability between case and control subjects, the current study adds weight to an accumulating body of evidence consistent with a protective effect of smoking on the development of PD. The demonstration of a significant dose-related association in this relatively small population with highly correlated smoking behaviors highlights the importance of further delineating the responsible mechanisms.

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