Cigarette Smoking and the Incidence of Parkinson's Disease in Two Prospective Studies

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An inverse association between cigarette smoking and idiopathic Parkinson's disease has been reported in several retrospective studies, but prospective evidence is available only for men. We assessed the association between the incidence of Parkinson's disease and smoking in two large prospective cohort studies comprising men and women. New cases of Parkinson's disease were identified in the Nurses' Health Study for 1976–1996, and in the Health Professionals Follow-up Study for 1986–1996. Smoking history was assessed at baseline and updated on subsequent biennial questionnaires. In women, the age-adjusted rate ratios (95% confidence intervals) for Parkinson's disease relative to never-smokers were 0.7 (0.5, 1.0) for past smokers, and 0.4 (0.2, 0.7) for current smokers. In men, the age-adjusted rate ratios for Parkinson's disease relative to never-smokers were 0.5 (0.4, 0.7) for past smokers, and 0.3 (0.1, 0.8) for current smokers. In both cohorts, the strength of the association decreased with time since quitting (among past smokers), increased with number of cigarettes per day (among current smokers), and increased with pack-years of smoking. These prospective findings confirm that an inverse association between smoking and the incidence of Parkinson's disease exists in both men and women.

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Virtually all case-control studies have found a strong inverse association between cigarette smoking and idiopathic Parkinson's disease (PD).[1–14] However, a number of arguments have been raised against the existence of a truly protective effect of smoking on the risk of PD.[1,15] These include confounding, selection bias, information bias, and reverse causation. Data from prospective studies of the incidence of PD are much less susceptible to some of these potential biases, but few such studies have been conducted.[16,17] In addition, data from prospective studies have not provided age-specific estimates of incidence by smoking status for women.

We report on the association between smoking and the incidence of PD in two large ongoing prospective studies including both women and men: the Nurses' Health Study (NHS) and the Health Professionals' Follow-Up Study (HPFS).

Patients and Methods

Patients

The NHS was established in 1976, when 121,700 female registered nurses from 11 states, aged 30 to 55 years, responded to a mailed questionnaire about disease history and lifestyle items. The HPFS was established in 1986, when 51,529 male health professionals (dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians) from all states, aged 40 to 75 years, responded to a similar questionnaire. Follow-up questionnaires are mailed to the participants of both studies every 2 years to update information on potential risk factors for chronic diseases and to ascertain whether major medical events have occurred. A specific question on the lifetime occurrence of PD was first included in the 1994 (NHS) and 1988 (HPFS) questionnaires. A question on PD diagnosis within the last 2 years was included in subsequent questionnaires. For this analysis, we excluded participants who had received a diagnosis of PD, stroke, or cancer before they answered the baseline questionnaire.

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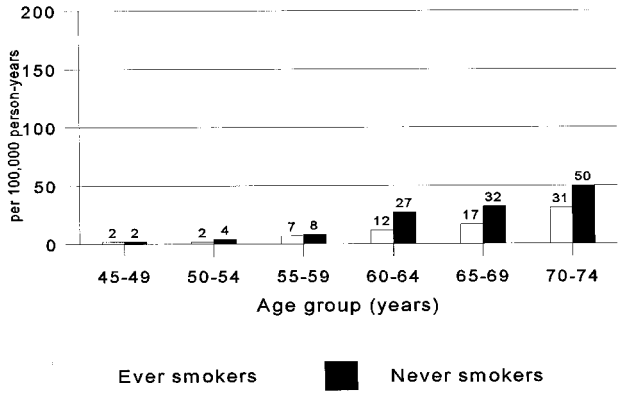


Fig 1. Incidence of Parkinson's disease among women.

Case Ascertainment

As previously described,[18] we requested permission to obtain relevant medical records from all participants who reported a new diagnosis of PD. After obtaining permission, we sent a questionnaire to the treating neurologists to confirm the diagnosis of primary idiopathic parkinsonism and the certainty of the diagnosis (definite, probable, or possible), and requested medical records. The questionnaire included details on date of first neurological symptoms, date of diagnosis, clinical signs, and response to treatment with L-dopa. If a neurologist was not involved or did not respond, we mailed the questionnaire to the patient's internist. The diagnosis was confirmed (definite or probable idiopathic PD) in 95% (NHS) and 88% (HPFS) of the self-reported cases by the treating physicians or by review of the medical records. We also requested death certificates of all deceased participants to search for possibly unreported diagnoses of PD. Only confirmed definite and probable diagnoses of idiopathic PD are used in this analysis.

Assessment of Exposure

A detailed lifetime smoking history was obtained at the beginning of the study and updated every 2 years, either up to 4 years before the diagnosis or to the date of first symptoms. Smoking status was defined as never, past, or current (if any amount of current smoking was reported). Cumulative exposure to cigarette smoking was summarized by multiplying the number of packs smoked per day (1 pack contains 20 cigarettes) by the number of years over which that amount was smoked (pack-years). Other covariates considered in the analyses included coffee and alcohol intake, as reported by the participants in the questionnaires. Caffeine intake was assessed at baseline using a semiquantitative food-frequency questionnaire, as previously reported.[18]

Statistical Analysis

Each participant contributed person-time of follow-up from the date of return of the baseline questionnaire to the date of PD diagnosis, death from any cause, or end of follow-up, whichever came first. For the rates presented here, end of follow-up was June 1996 for the NHS and February 1996 for the HPFS. Age-specific incidence rates were calculated as the number of PD cases (definite and probable only) divided by person-time of follow-up in each age group. We estimated Mantel–Haenszel age-adjusted incidence rate ratios (RR) and their 95% confidence intervals (CI). A Wald test was used to test for heterogeneity of RR between the 2 studies. Log RR from the 2 studies were weighted by the inverse of their variances to obtain a pooled estimate. We used time-dependent Cox proportional hazards regression to estimate RR and CI for smoking status and pack-years of smoking, adjusted for age and other covariates.

Separate analyses were performed according to date of first symptoms, defined as the earliest date at which neurological symptoms attributable to PD were reported by the participant or by the participant's physician. In those analyses, participants who reported that their symptoms started before the baseline were excluded.

Results

We documented 153 new physician-confirmed diagnoses of PD during the 20 years of follow-up in NHS, and 146 during the 10 years of follow-up in HPFS. There were 152 PD cases in the NHS, and 128 in the HPFS, with first symptoms during the follow-up period. Only 4 cases (2.6% of the total) in the NHS, and 1 case (0.7%) in the HPFS were identified from death certificates.

The incidence of PD rose sharply after age 60 and was higher among men than among women for all age groups, both among never-smokers (Fig 1) and ever-smokers (Fig 2). These rates were similar to others previously reported.[19–21]

In both cohorts, smoking was associated with a lower incidence of PD (Table 1). The pooled RR for current smokers compared with never-smokers was 0.4 (95% CI: 0.2, 0.6). The RR (95% CI) were 0.5 (0.2, 0.9) for smokers of between 1 and 14 cigarettes per day, and 0.3 (0.2, 0.6) for smokers of 15 or more cigarettes per day, compared with never-smokers. The pooled RR (95% CI) for past smokers was 0.6 (0.5, 0.8), compared with never-smokers. By time since quitting smoking, the RR were 0.7 (0.5, 0.9) for 10 or more years, and 0.3 (0.2, 0.6) for less than 10 years.

Fig 2. Incidence of Parkinson's disease among men.

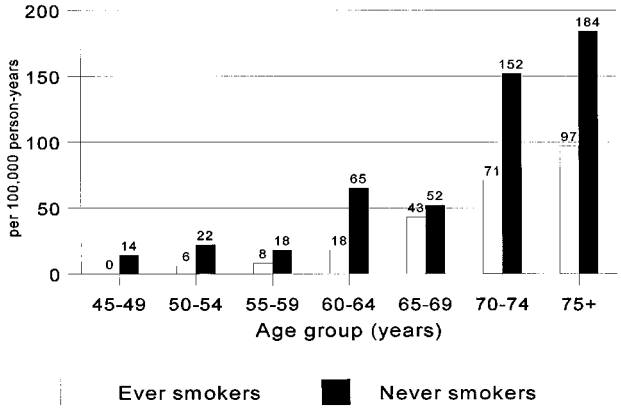


Table 1. Relative Rates and 95% Confidence Intervals for the Diagnosis of Parkinson's Disease by Smoking[a]

Cohort	Smoking Status	No. Cases	Person-Years	RR (95% CI)
NHS[b]	Never-smoker	87	988,491	1.0 (ref.)
	Past smoker	51	722,971	0.7 (0.5, 1.0)
	Quit ≥10 yr ago	46	473,454	0.9 (0.6, 1.3)
	Quit <10 yr ago	5	243,509	0.2 (0.1, 1.6)
	Current smoker	15	574,802	0.4 (0.2, 0.7)
	1–14 cigarettes/day	6	172,071	0.5 (0.2, 1.1)
	≥15 cigarettes/day	9	393,302	0.4 (0.2, 0.7)
HPFS[c]	Never-smoker	88	207,270	1.0 (ref.)
	Past smoker	51	182,408	0.5 (0.4, 0.7)
	Quit ≥10 yr ago	42	139,577	0.5 (0.4, 0.8)
	Quit <10 yr ago	6	38,293	0.4 (0.2, 0.9)
	Current smoker	4	35,978	0.3 (0.1, 0.8)
	1–14 cigarettes/day	2	10,518	0.4 (0.1, 1.6)
	≥15 cigarettes/day	1	18,605	0.1 (<0.1, 1.0)
Pooled[d]	Never-smoker			1.0 (ref.)
	Past smoker			0.6 (0.5, 0.8)
	Quit ≥10 yr ago			0.7 (0.5, 0.9)
	Quit <10 yr ago			0.3 (0.2, 0.6)
	Current smoker			0.4 (0.2, 0.6)
	1–14 cigarettes/day			0.5 (0.2, 0.9)
	≥15 cigarettes/day			0.3 (0.2, 0.6)

[a]Adjusted for age (5-year categories).
[b]Smoking information was missing for 4,691 person-years.
[c]Smoking information was missing for 24,764 person-years, including 3 cases.
[d]p Values from Wald tests for heterogeneity of RR were 0.24, 0.05, 0.44, 0.56, 0.96, and 0.39 for past, quit <10 years ago, quit ≥10 years ago, current smokers, 1–14 cigarettes/day, and ≥15 cigarettes/day, respectively.

RR = relative rate; CI = confidence interval; NHS = Nurses' Health Survey; HPFS = Health Professionals' Follow-Up Study.

Similar RR (95% CI) were obtained for first symptoms of PD: 0.3 (0.2, 0.6) for current smokers, and 0.6 (0.5, 0.8) for past smokers, versus never-smokers.

The incidence of PD decreased with the number of pack-years smoked (p <0.001, Table 2). Smokers of 45 or more pack-years had the lowest incidence of PD compared with never-smokers. The pooled RR (95% CI) was 0.4 (0.3, 0.6) for both diagnosis and first symptoms of PD.

When restricting analysis to cases that had been confirmed by a neurologist (86% of cases in NHS and 75% in HPFS), the pooled RR were almost identical to those reported above. We repeated all analyses with a more restrictive case definition (ie, only PD-definite cases) and again found almost identical pooled RR. Compared with never-smokers, the pooled RR (95% CI) were 0.4 (0.2, 0.6) for current smokers and 0.6 (0.5, 0.8) for past smokers. The corresponding RR (95% CI) for categories of pack-years were 0.9 (0.6, 1.4) for 1 to 9 years, 0.7 (0.4, 1.0) for 10 to 24 years, 0.4 (0.3, 0.6) for 25 to 44 years, and 0.4 (0.2, 0.6) for more than 45 years. The pooled RR for smoking status were similar for participants under 65 years of age, although the CIs were wider due to the smaller number of cases. Age of starting smoking was not significantly associated with the incidence of PD in pooled analyses.

Statistical adjustment for alcohol and caffeine intake had little effect on the results. Because we have previously reported an inverse association between caffeine consumption and PD risk,[18] we evaluated the association between smoking and PD within 2 groups defined by daily caffeine consumption at baseline: less than 150mg and more than 150mg (1 cup of coffee contains ~150mg). The strength of the association was similar in both groups (Table 3). Compared with never-smokers, the pooled RR (95% CI) for smokers of more than 24 pack-years was 0.4 (0.2, 0.6) among those who consumed less than 150mg of caffeine per day, and 0.5 (0.3, 0.7) among those who consumed more than 150mg caffeine per day.

The mean age at first symptoms was 61.3 years (SD 7.0) among ever-smokers and 62.2 years (SD 6.3) among never-smokers in the NHS (p = 0.96; analysis of covariance adjusted for age at entry in the study), and 68.3 years (SD 7.5) among ever-smokers and 65.3 years (SD 10.1) among never-smokers in the HPFS (p = 0.81).

Compared with never-smokers, the age-adjusted relative mortality rate was 1.4 (95% CI: 1.3, 1.5) for past smokers and 2.1 (2.0, 2.3) for current smokers in women, and 1.3 (1.2, 1.4) for past smokers and 2.3 (2.1, 2.6) for current smokers in men. Mortality increased with age and was greater among smokers than among nonsmokers in all age groups (Figs 3 and 4).

Table 2. Relative Rates and 95% Confidence Intervals for the Diagnosis of Parkinson's Disease by Pack-years of Smoking, Current and Past Smokers Combined[a]

Cohort/Smoking Status/ Pack-Years	No. Cases	Person-Years	RR (95% CI)	*p*
NHS[b]				
Never-smoker	87	988,491	1.0 (ref.)	
1–9	19	283,100	1.0 (0.6, 1.6)	
10–24	19	366,148	0.8 (0.5, 1.3)	
25–44	12	378,018	0.4 (0.2, 0.7)	
≥45	15	250,257	0.4 (0.3, 0.7)	<0.001
HPFS[c]				
Never-smoker	88	207,270	1.0 (ref.)	
1–9	10	40,469	0.6 (0.3, 1.2)	
10–24	17	77,251	0.5 (0.3, 0.8)	
25–44	16	57,848	0.5 (0.3, 0.9)	
≥45	8	32,786	0.3 (0.2, 0.7)	<0.001
Pooled[d]				
Never-smoker			1.0 (ref.)	
1–9			0.8 (0.6, 1.2)	
10–24			0.6 (0.4, 0.9)	
25–44			0.5 (0.3, 0.7)	
≥45			0.4 (0.3, 0.6)	<0.001

[a]Adjusted for age (5-year categories).
[b]Total of 24,940 person-years, including 1 case, with missing pack-years information.
[c]Total of 33,437 person-years, including 7 cases, with missing pack-years information.
[d]*p* Values from Wald tests for heterogeneity of RR were 0.26, 0.22, 0.52, and 0.61 for 1–9, 10–24, 25–44, and ≥45 pack-years, respectively.

Discussion

Our findings support the existence of a strong inverse association between cigarette smoking and the risk of idiopathic PD. Compared with never-smokers, the incidence of PD was 60% lower among current smokers, and 40% lower among past smokers. The risk decreased with number of cigarettes smoked among current smokers, and increased with years since quitting smoking among past smokers. Similar associations were found for women and men.

An inverse association between PD and smoking, which was first detected in mortality studies,[22–26] has been found in virtually all case-control studies reported.[1–14] Little information is available, however, from follow-up studies that identify incident PD cases. The incidence of PD was 60% lower among ever-

Table 3. Relative Rates and 95% Confidence Intervals for the Diagnosis of Parkinson's Disease by Smoking and Caffeine Intake[a]

		<150mg Caffeine/Day			≥150mg Caffeine/Day		
Cohort	Pack-Years	No. Cases	Person-Years	RR (95% CI)	No. Cases	Person-Years	RR (95% CI)
NHS[b]	0	23	161,937	1.0 (ref.)	51	442,551	1.0 (ref.)
	1–9	7	36,973	1.6 (0.7, 3.7)	11	138,669	0.9 (0.5, 1.8)
	10–24	2	39,995	0.4 (0.1, 1.6)	12	172,531	0.8 (0.4, 1.5)
	≥25	2	59,167	0.2 (<0.1, 0.8)	16	328,202	0.4 (0.2, 0.7)
HPFS[c]	0	58	114,797	1.0 (ref.)	26	86,311	1.0 (ref.)
	1–9	8	18,796	0.8 (0.4, 1.7)	2	20,671	0.4 (0.1, 1.5)
	10–24	2	33,217	0.6 (0.3, 1.1)	5	41,834	0.4 (0.2, 1.0)
	≥25	10	33,625	0.4 (0.2, 0.7)	14	54,483	0.6 (0.3, 1.2)
Pooled[d]	0			1.0 (ref.)			1.0 (ref.)
	1–9			1.1 (0.6, 0.9)			0.8 (0.4, 1.4)
	10–24			0.6 (0.3, 1.0)			0.6 (0.4, 1.1)
	≥25			0.4 (0.2, 0.6)			0.5 (0.3, 0.7)

[a]Adjusted for age (5-year categories). NHS include cases diagnosed after 1980 (first dietary assessment) only.
[b]Total of 12,637 person-years, including 1 case, with missing pack-years information.
[c]Total of 31,875 person-years, including 7 cases, with missing pack-years information.
[d]*p* Values from Wald tests for heterogeneity of RR were 0.23, 0.60, 0.36 (<150mg) and 0.29, 0.22, 0.37 (≥150mg) for 1–9, 10–24, and ≥45 pack-years, respectively.

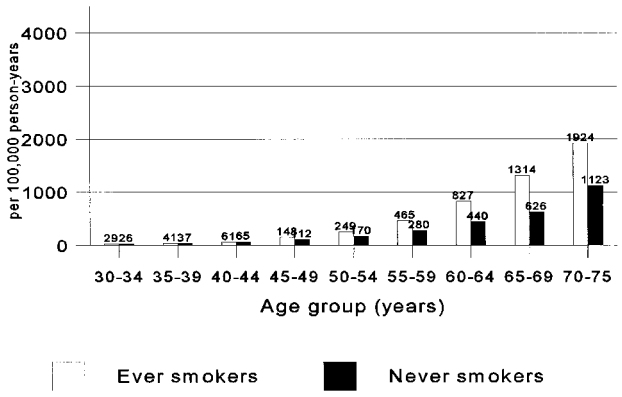


Fig 3. Mortality rate among women.

smokers compared with never-smokers in the Honolulu Heart Program, a cohort study of 8,006 men of Japanese and Okinawan ancestry born between 1909 and 1919 who resided in Oahu, Hawaii, in 1965.[17] (Another prospective study has reported but not quantified an inverse association between smoking and PD.[16]) Our results, based on two of the largest series of prospectively identified PD cases, confirm the results of previous case-control and cohort investigations, and apply to both men and women.

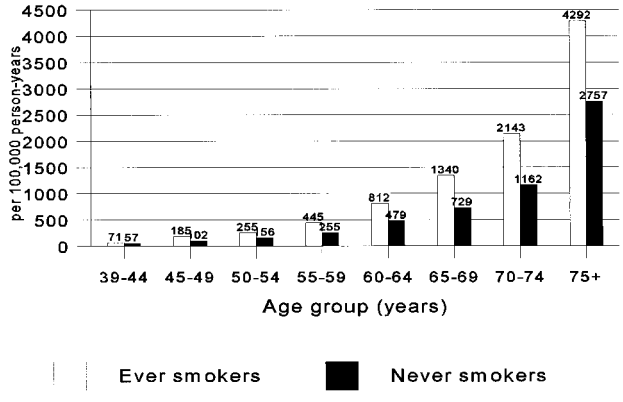
The key question is whether this strong inverse association reflects a truly protective effect of smoking on the risk of developing PD, or whether there are alternate noncausal explanations. Several biological theories of PD that are consistent with smoking protection have been summarized by Morens and colleagues.[1] These theories include (1) a direct chemical protective effect of smoking, mediated through the stimulation of dopamine release and upregulation of nicotinic receptors induced by nicotine; (2) protection against toxic neuronal damage conferred by smoking, perhaps by inhibition of the potentially toxic-generating enzyme MAOB or by competitive inhibition of neurotoxins binding to nicotinic receptors; and (3) smoking-associated inhibition of free radical damage to nigral cells mediated through CO, which appears to be protective against the membrane damage induced by H_2O_2.

Proposed alternative explanations to the inverse association between smoking and PD are that (1) PD diagnoses are more frequently omitted in the death certificates and medical records of smokers (information bias); (2) there is an increased mortality of younger smokers from causes other than PD (selection bias); (3) smoking and PD share common genetic or environmental causes (confounding); and (4) patients predisposed to develop PD or with preclinical PD are less susceptible to smoking or are more likely to quit (reverse causation).

The information bias due to a differential misclassification of PD diagnoses by smoking status is referred to as "diagnostic displacement."[1] According to this hypothesis, smokers' medical charts and death certificates would be so overwhelmed by diagnoses of other smoking-related diseases that the diagnosis of PD, which may be perceived as a less serious condition or one that did not lead to death, is not always recorded. Although this possibility cannot be ruled out in mortality and certain case-control studies, it is highly unlikely in follow-up studies[16,17] in which cases of PD are actively sought among the participants, and even more in our studies of health professionals.

There are a number of variations of the hypothesis that selection bias due to mortality can explain the inverse association between smoking and PD. Briefly, this hypothesis states that smokers with PD die younger than smokers without PD. As case-control studies using prevalent cases are only able to identify those PD patients alive at the time of the study, nonsmokers would be guaranteed to be overrepresented among those surviving cases. Obviously, this explanation does not apply to follow-up studies that follow participants who have not yet developed PD and that identify incident PD cases continuously. A more refined version of the selection bias hypothesis is that smokers who are genetically predestined to develop PD die young from smoking-related diseases, perhaps even before the first recognizable signs of PD appear.[15] A strong argument against the existence of this differential survival is that smoking has been associated with a lower incidence of PD in studies of monozygotic twins, in which both twins in each pair possess the same nuclear genes and are of the same age.[27,28] In our data, as expected, smokers had higher mortality than occurred among nonsmokers in all age groups, and because of premature death smokers would have a lower lifetime risk of PD. Nevertheless, this differential mortality cannot explain the lower incidence rate of PD in smokers compared with nonsmokers of the same age across all age groups, including people under age 60 who have a

Fig 4. Mortality rate among men.



relatively low overall mortality. (This was also observed in the Honolulu Heart Program.)[29]

Confounding seems an unsatisfactory explanation for the magnitude of the association. A number of candidate genes for smoking behavior have been identified[30,31] but none of these have been independently linked to an increased risk of PD; and adjustment for lifestyle correlates of smoking behavior, such as coffee and alcohol intake, had negligible effects on the association between smoking and PD in our studies and in a previous prospective study.[17] Furthermore, the hypothesized common cause should be constant across ethnic groups and geographical locations, the magnitude of its association with both smoking and PD should be very large to induce such a strong inverse association,[32] and it should preserve the observed dose-response and time-since-quitting relations with the risk of PD. All of the above greatly diminishes the probability that such a strong hypothetical confounder has not yet been identified.

There are also several versions of the argument claiming the existence of a causal effect of PD on smoking behavior, rather than a protective effect of smoking on PD. That first symptoms of PD induce quitting smoking is not very convincing, as we found an inverse relation even when we used smoking status before first symptoms of the disease and even among people who quit smoking more than 10 years before first symptoms. Hence, if smoking is affected by PD, and not the other way around, some forms of PD must already be present—but subclinical—in the first decades of life, manifesting themselves only as the person ages. A further elaboration of this hypothesis is that PD patients have a characteristic pre-existing personality (moralistic, law-abiding, conscientious, risk averse) that avoids smoking, or an underlying metabolism (genetic or as a result of a toxic insult early in life) that makes smoking particularly unrewarding.[33] This hypothesis is remarkably difficult to test. A finding that seems to go against the hypothesis of aversion to addictive behaviors as one of the first symptoms of the disease is that PD patients did not drink less alcohol than other members of the cohort in the Honolulu Heart Program and in our studies (data not shown). Another piece of indirect evidence against this hypothesis is a reported improvement, or at least not worsening, of parkinsonian symptoms after smoking.[34–41] However, some recent studies suggest that smoking may also accentuate parkinsonian symptoms in some patients.[42–45]

In summary, we present age-specific incidence rates of PD by smoking status that are consistent with a protective effect of cigarette smoking on the risk of PD in both men and women, although the existence of aversion to smoking among predestined PD patients cannot be excluded. Other alternatives, such as confounding, diagnostic displacement, and selective mortality, seem much less likely explanations of this strong inverse association. Of course, any public health benefits of smoking derived from a potential reduction of the incidence of PD would be overwhelmed by its detrimental effects on conditions such as cancer and cardiovascular disease. The chief interest of elucidating the role of smoking on PD is to enhance our understanding of the pathogenesis of the disease, which may lead to preventive or therapeutic advancements.

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References

1. Morens DM, Grandinetti A, Reed D, et al. Cigarette smoking and protection from Parkinson's disease. Neurology 1995;45: 1041–1051.
2. Morano A, Jiménez-Jiménez FJ, Molina JA, Antolín MA. Risk factors for Parkinson's disease: case-control study in the province of Cáceres, Spain. Acta Neurol Scand 1994;89:164–170.
3. De Michele G, Filla A, Volpe G, et al. Environmental and genetic risk factors in Parkinson's disease: a case-control study in southern Italy. Mov Disord 1996;11:17–23.
4. Liou HH, Tsai MC, Chen CJ, et al. Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. Neurology 1997;48:1583–1588.
5. Hellenbrand W, Seidler A, Robra B-P, et al. Smoking and Parkinson's disease: a case-control study in Germany. Int J Epidemiol 1997;26:328–339.
6. Smargiassi A, Mutti A, De Rosa A, et al. A case-control study of occupational and environmental risk factors for Parkinson's disease in the Emilia–Romagna Region of Italy. Neurotoxicology 1998;19:709–712.
7. McCann SJ, LeCouteur DG, Green AC, et al. The epidemiology of Parkinson's disease in an Australian population. Neuroepidemiology 1998;17:310–317.
8. Chan DKY, Woo J, Ho SC, et al. Genetic and environmental risk factors for Parkinson's disease in a Chinese population. J Neurol Neurosurg Psychiatry 1998;65:781–784.
9. Fall P-A, Fredrikson M, Axelson O, Granérus A-K. Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. Mov Disord 1999;14:28–37.
10. Gorell JM, Rybicki A, Johnson CC, Peterson EL. Smoking and Parkinson's disease: a dose-response relationship. Neurology 1999;52:115–119.
11. Taylor CA, Saint-Hilaire MH, Cupples LA, et al. Environmental. medical, and family history risk factors for Parkinson's disease: a New England-based case-control study. Am J Hum Genet 1999;1999:742–749.
12. Kuopio A-M, Marttila RJ, Helenius H, Rinne UK. Environmental risk factors in Parkinson's disease. Mov Disord 1999; 14:928–939.
13. Tzourio C, Rocca WA, Breteler MM, et al. Smoking and Parkinson's disease: an age-dependent risk effect? Neurology 1997; 49:1267–1272.

14. Mayeux R, Tang M-X, Marder K, et al. Smoking and Parkinson's disease. Mov Disord 1994;9:207–212.
15. Riggs JE. The "protective" influence of cigarette smoking on Alzheimer's and Parkinson's diseases. Quagmire or opportunity for neuroepidemiology. Neurol Clin 1996;14:353–358.
16. Wolf PA, Feldman RG, Saint-Hilaire M, et al. Precursors and natural history of Parkinson's disease: the Framingham Study. Neurology 1991;41(suppl 1):371.
17. Grandinetti A, Morens DM, Reed D, MacEachern D. Prospective study of cigarette smoking and the risk of developing idiopathic Parkinson's disease. Am J Epidemiol 1994;139: 1129–1138.
18. Ascherio A, Zhang SM, Hernán MA, et al. Prospective study of caffeine consumption and the risk of Parkinson's disease in men and women. Ann Neurol 2001;0:56–63.
19. Mayeux R, Marder K, Cote LJ, et al. The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988–1993. Am J Epidemiol 1995;142: 820–827.
20. Morens DM, Davis JW, Grandinetti A, et al. Epidemiologic observations on Parkinson's disease: incidence and mortality in a prospective study of middle-aged men. Neurology 1996;46: 1044–1050.
21. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976–1990. Neurology 1999;52:1214–1220.
22. Kahn HA. The Dorn Study of smoking and mortality among U.S. veterans: report on eight and one-half years of observation. In: Haenszel W, ed. Epidemiological approaches to the study of cancer and other chronic diseases. National Cancer Institute Monograph. Vol 19. Bethesda, MD: US Department of Health, Education, and Welfare, 1966:1–27.
23. Hammond EC. Smoking in relation to the death rates of one million men and women. In: Haenszel W, ed. Epidemiological approaches to the study of cancer and other chronic diseases. National Cancer Institute Monograph. Vol 19. Bethesda, MD: US Department of Health, Education, and Welfare, 1966: 127–204.
24. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. BMJ 1976;2:1525–1536.
25. Doll R, Peto R, Wheatley K, et al. Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ 1994;309:901–911.
26. Hirayama Y. Epidemiological patterns of Parkinson's disease based on a cohort study [in Japanese]. In: Epidemiology of intractable diseases. Research Committee, ed. Tokyo: Japan Ministry of Health and Welfare, 1985:219–227.
27. Bharucha NE, Stokes L, Schoenberg BS, et al. A case-control study of twin pairs discordant for Parkinson's disease: a search for environmental risk factors. Neurology 1986;36:284–288.
28. Duvoisin RC, Elridge R, Williams A, et al. Twin study of Parkinson disease. Neurology 1981;31:77–80.
29. Morens DM, Grandinetti A, Davis J, et al. Evidence against the operation of selective mortality in explaining the association between cigarette smoking and reduced occurrence of idiopathic Parkinson disease. Am J Epidemiol 1996;144:400–404.
30. Pianezza ML, Sellers EM, Tyndale RF. Nicotine metabolism reduces smoking. Nature 1998;393:750.
31. Rossing MA. Genetic influences on smoking: candidate genes. Environ Health Perspect 1998;106:231–238.
32. Walker AM. Observation and inference: an introduction to the methods of epidemiology. Newton Lower Falls, MA: Epidemiology Resources, 1991.
33. Paulson GW, Dadmehr N. Is there a premorbid personality typical for Parkinson's disease? Neurology 1991;41(suppl 2): 73–76.
34. Moll H. The treatment of post-encephalitic parkinsonism by nicotine. BMJ 1926;1:1079–1081.
35. Vartiainen I. Die atropinbehandlung des folgezustandes der encephalitis epidemica. Acta Med Scand 1944;116:536–560.
36. Marshall J, Schnieden H. Effect of adrenaline, noradrenaline, atropine, and nicotine on some types of human tremor. J Neurol Neurosurg Psychiatry 1966;29:214–218.
37. Ishikawa A, Miyatake T. Effects of smoking in patients with early-onset Parkinson's disease. J Neurol Sci 1993;117:28–32.
38. Koller W, Herbster G. Nicotine and tremor. Neurology 1988; 38(suppl 1):313.
39. Burtscher M, Likar R, Pechlaner C, et al. Motor symptoms similar to parkinsonism in heavy smokers. Int J Sports Med 1994;15:207–212.
40. Fagerström KO, Pomerleau O, Giordani B, Stelson F. Nicotine may relieve symptoms of Parkinson's disease. Psychopharmacology 1994;116:117–119.
41. Clemens P, Baron JA, Coffey D, Reeves A. The short-term effect of nicotine chewing gum in patients with Parkinson's disease. Psychopharmacology 1994;117:253–256.
42. Miwa H, Mizuno Y. Dystonia preceding dopa-responsive parkinsonism. No to Shinkei. Brain Nerve 1996;48:149–154.
43. Nishimura H, Tachibana H, Okuda B, Sugita M. Transient worsening of Parkinson's disease after cigarette smoking. Intern Med 1997;36:651–653.
44. Nilsson A, Waller L, Rosengren A, et al. Cigarette smoking is associated with abnormal involuntary movements in the general male population—a study of men born in 1933. Biol Psychiatry 1997;41:717–723.
45. Ebersbach G, Stöck M, Müller J, et al. Worsening of motor performance in patients with Parkinson's disease following transdermal nicotine administration. Mov Disord 1998;14: 1011–1013.