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Original Contribution

Lifestyle, Family History, and Risk of Idiopathic Parkinson Disease: A Large Danish Case-Control Study

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The relationship between Parkinson disease (PD) and smoking has been examined in several studies, but little is known about smoking in conjunction with other behaviors and a family history of PD. Using unconditional logistic regression analysis, we studied individual and joint associations of these factors with idiopathic PD among 1,808 Danish patients who were diagnosed in 1996–2009 and matched to 1,876 randomly selected population controls. Although there was a downward trend in duration of smoking, this was not observed for daily tobacco consumption. A moderate intake of caffeine (3.1–5 cups/day) was associated with a lower odds ratio for PD (0.45, 95% confidence interval: 0.34, 0.62), as was a moderate intake of alcohol (3.1–7 units/week) (odds ratio = 0.60, 95% confidence interval: 0.58, 0.84); a higher daily intake did not reduce the odds further. When these behaviors were studied in combination with smoking, the odds ratios were lower than those for each one alone. Compared with never smokers with no family history of PD, never smokers who did have a family history had an odds ratio of 2.81 (95% confidence interval: 1.91, 4.13); for smokers with a family history, the odds ratio was 1.60 (95% confidence interval: 1.15, 2.23). In conclusion, duration of smoking seems to be more important than intensity in the relationship between smoking and idiopathic PD. The finding of lower risk estimates for smoking in combination with caffeine or alcohol requires further confirmation.

alcohol drinking; caffeine; case-control study; lifestyle; Parkinson disease; smoking

Abbreviations: ICD, *International Classification of Diseases*; IPD, idiopathic Parkinson disease; PD, Parkinson disease.

After the first report of a lower mortality rate from Parkinson disease (PD) among smokers in 1959 (1), many studies confirmed that inverse association, noting a duration-dependent reduction in risk (2–5). A lower risk of PD among coffee drinkers has also been demonstrated (6–10), although the association is not as consistent and strong as that for cigarette smoking. An inverse relationship between alcohol consumption and PD has been suggested; although multiple large prospective cohort studies failed to demonstrate an association (11–13), a lower risk among alcohol drinkers was found in a recent meta-analysis (14). These behaviors are often concurrent (15), but little is known about the association of PD with smoking in the context of regular intakes of caffeine-containing coffee and alcohol. Because cigarette smoking can accelerate the metabolism and clearance of caffeine in humans (16) and alcohol affects nicotinic acetylcholine receptors in the brain (17), it is conceivable that smoking modifies the associations of caffeine and alcohol consumption with PD.

An inherited predisposition is considered to play an etiological role in PD (18), and several studies have shown a strong familial aggregation of the disease (19). In 2 small case-control studies of the interaction between smoking and a family history of PD, however, divergent results were obtained (18, 20). In the present case-control study, we assessed the individual and combined associations of cigarette smoking, caffeine intake, and alcohol consumption with a family history of PD in a large group of patients with idiopathic Parkinson disease (IPD).

Table 1. Descriptive Characteristics of 1,808 Patients With Idiopathic Parkinson Disease and 1,876 Population Controls, Denmark, 2008–2010

Characteristic	Patients ($n = 1,808$)				Controls ($n = 1,876$)	
	No.	%	Median	Range	No.	%
Women	741	41.0			760	40.5
Men	1,067	59.0			1,116	59.5
Age at interview, years			69	39–89		
Age at first cardinal symptom of IPD, years			62	28–85		
Highest attained educational level						
Basic school/high school (7–12 years)	427	23.6			428	22.8
Vocational school (10–12 years)	870	48.1			930	49.6
Higher (≥13 years)	511	28.3			518	27.6
Degree of urbanization						
Capital area	441	24.4			559	29.8
Provincial city	1,115	61.7			962	51.3
Rural area	167	9.2			208	11.1
Peripheral region	82	4.5			146	7.8
Living abroad	3	0.2			1	0.1

Abbreviation: IPD, idiopathic Parkinson disease.

METHODS

Patients

From the files of the Danish National Hospital Register, we identified 2,762 patients who were 35 years of age or older, had been discharged from 1 of the 10 major neurological treatment centers in Denmark with a primary diagnosis of PD (*International Classification of Diseases* (ICD), *Eight Revision* code 342 and ICD, *Tenth Revision* code G20) in 1996–2009, and were alive for interview between January 2008 and December 2010. We included patients who were younger than 70 years of age at diagnosis before 2002 and younger than 80 years at diagnosis in 2002 or later to ensure that most of the eligible patients would have survived to the time of interview. Of the 2,762 patients identified, we excluded 179 (6%) patients whose medical records before the interview precluded a diagnosis of PD or who denied having PD at the interview. Of the remaining 2,583 patients, 2,086 (81%) agreed to be interviewed, and we obtained medical records for 2,066 (99%) of them. In order to distinguish cases of IPD from other forms of parkinsonism, the medical records were reviewed rigorously by trained reviewers who were supervised by a movement disorder specialist. The reviewers applied the standard diagnostic criteria of the United Kingdom Brain Bank (21) and the criteria of Gelb et al. (22) to all 2,066 medical records. The varying degrees of completeness of the medical records necessitated some flexibility in the evaluation, but in general, we considered a case of PD to be idiopathic if 1) at least 2 of 4 cardinal symptoms (resting tremor, bradykinesia, rigidity, and asymmetrical onset) were present; 2) the patient responded positively to antiparkinsonian medication; 3) the patient had no atypical features (dementia before development of cardinal symptoms, early falls, severe symptomatic dysautonomia, rapid progression of the disease, sudden onset of symptoms, supranuclear gaze palsy, hallucinations unrelated to medication, freezing phenomena, of Babinsky sign); and 4) there was no sign of a differential diagnosis, for example, cerebrovascular disease. After application of these criteria, 1,828 (88.5%) of the 2,066 interviewed patients were considered to have IPD (Web Figure 1, available at http://aje.oxfordjournals.org/).

Population control subjects

For each of the 2,583 patients initially contacted for interview, 5 potential control subjects were randomly selected from the Danish Central Population Register. The control subjects were alive and had no prior hospital diagnosis of PD at the index date (date of first hospital contact for PD of their respective case), and they were matched to the PD case on sex and year of birth. We contacted the control subjects by phone in random order until 1 consented to participate. Of the 3,626 who were contacted, 1,909 (53%) consented to participate and completed an interview (Web Figure 1).

Exclusions of patients and control subjects

We showed previously that PD patients, in collaboration with their primary health care physician, start treatment with anti-Parkinson drugs an average of 3 years before their first hospital contact for PD (23). Thus, in order to further reduce the likelihood of including people with neurological conditions unrelated to IPD, we excluded 14 patients and 22 control subjects who had had a hospital contact for dementia (ICD Eighth Revision codes 290.09–290.19 and 293.09; ICD Tenth Revision codes F00-03, F05.1, and G30) or cerebrovascular disease (ICD Eighth Revision codes 430–438; ICD Tenth Revision codes I60–69, G45, and G46) any time

Table 2. Odds Ratios for Idiopathic Parkinson Disease by Smoking Behavior, Denmark, 2008–2010

Smoking Behavior	At Date of First Cardinal Symptom ($n = 3,684$)						10 Years Before First Cardinal Symptom ($n = 3,684$)					
	No. of Patients	No. of Controls	Primary Adjusted Analyses[a]		Secondary Adjusted Analyses[b]		No. of Patients	No. of Controls	Primary Adjusted Analyses[a]		Secondary Adjusted Analyses[b]	
			OR	95% CI	OR	95% CI			OR	95% CI	OR	95% CI
Cigarette smoking status												
Never smoker	909	667	1.00	Referent	1.00	Referent	909	667	1.00	Referent	1.00	Referent
Ever smoker	899	1,209	0.53	0.46, 0.61	0.55	0.48, 0.63						
Former smoker	750	833	0.65	0.56, 0.75	0.67	0.58, 0.78						
Current smoker	149	376	0.28	0.23, 0.35	0.29	0.23, 0.37						
No. of cigarettes smoked per day												
0.1–9	260	304	0.62	0.51, 0.75	0.66	0.54, 0.81	253	308	0.59	0.49, 0.72	0.63	0.52, 0.77
10–19	274	416	0.47	0.39, 0.57	0.50	0.42, 0.61	273	408	0.48	0.40, 0.58	0.52	0.43, 0.63
20–29	129	164	0.55	0.43, 0.71	0.60	0.46, 0.79	134	163	0.58	0.45, 0.75	0.62	0.48, 0.81
≥30	29	42	0.48	0.29, 0.78	0.58	0.35, 0.96	29	41	0.49	0.30, 0.80	0.58	0.35, 0.98
P for trend[c]			0.20		0.46				0.50		0.70	
Years of smoking												
0–9	134	134	0.71	0.55, 0.93	0.74	0.56, 0.97	143	144	0.71	0.55, 0.91	0.74	0.57, 0.96
10–19	164	158	0.74	0.58, 0.95	0.84	0.66, 1.08	188	196	0.69	0.55, 0.87	0.78	0.62, 0.99
20–29	141	175	0.58	0.45, 0.74	0.63	0.49, 0.80	169	258	0.47	0.38, 0.58	0.50	0.40, 0.63
30–39	127	210	0.43	0.34, 0.55	0.46	0.36, 0.59	122	224	0.39	0.30, 0.49	0.40	0.31, 0.52
≥40	143	273	0.37	0.29, 0.46	0.38	0.30, 0.48	84	122	0.47	0.35, 0.64	0.48	0.35, 0.66
P for trend[c]			<0.001		<0.001				<0.001		<0.001	
Pack-years of smoking												
0.1–9	310	328	0.68	0.56, 0.82	0.73	0.60, 0.89	322	368	0.63	0.52, 0.75	0.68	0.56, 0.82
10–19	173	212	0.58	0.46, 0.73	0.63	0.50, 0.79	199	254	0.56	0.45, 0.69	0.60	0.48, 0.74
20–29	82	154	0.38	0.29, 0.51	0.40	0.30, 0.54	73	159	0.33	0.24, 0.44	0.36	0.27, 0.49
30–39	60	122	0.35	0.25, 0.48	0.37	0.27, 0.52	50	77	0.45	0.31, 0.66	0.46	0.31, 0.67
≥40	67	110	0.42	0.31, 0.59	0.45	0.32, 0.63	45	62	0.50	0.33, 0.75	0.55	0.36, 0.84
P for trend[c]			<0.001		<0.001				0.004		0.006	
Age at smoking cessation for former smokers												
<30	137	142	0.69	0.53, 0.89	0.72	0.55, 0.93	142	149	0.68	0.53, 0.88	0.71	0.55, 0.92
30–39	153	129	0.85	0.65, 1.09	0.93	0.71, 1.21	172	165	0.75	0.59, 0.95	0.82	0.64, 1.04
40–49	131	166	0.56	0.43, 0.72	0.62	0.48, 0.80	165	200	0.59	0.46, 0.74	0.64	0.51, 0.82
50–59	127	138	0.66	0.50, 0.85	0.70	0.54, 0.92	106	153	0.49	0.37, 0.64	0.51	0.39, 0.68
≥60	74	142	0.36	0.27, 0.49	0.38	0.28, 0.52	37	47	0.54	0.35, 0.85	0.57	0.36, 0.92
P for trend[c]			<0.001		0.003				0.02		0.031	

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Adjusted for sex and year of birth.
[b] Adjusted for sex, year of birth, age at first cardinal symptom, highest attained educational level, caffeine intake, alcohol consumption, family history of Parkinson disease, and level of urbanization.
[c] Linear trends were tested using the Wald test.

between the start of the Hospital Register in 1977 and up to 3 years before the index date. We excluded 1 further patient who, according to the medical record, appeared to have the onset of symptoms after the date of the interview. Finally, we excluded 5 patients and 11 control subjects for whom there was no information on smoking status, resulting in 1,808 IPD patients and 1,876 population controls for the analyses.

Lifestyle habits and family history of PD

Information on lifestyle habits and family histories of PD was obtained in structured telephone interviews. People with speaking difficulties were offered the choice of responding to the questionnaire by mail (16.8%). The questions on cigarette smoking covered smoking status at interview, age at the start

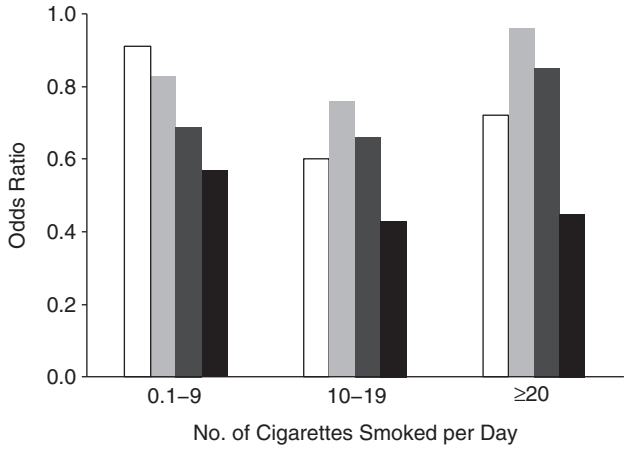

Figure 1. Odds ratios for idiopathic Parkinson disease in a combined analysis of number of cigarettes smoked per day and duration of smoking, Denmark, 2008–2010. Never smokers were used as the reference group. *P* values for linear trend (based on the Wald statistical test) across intensity of smoking within each duration category were as follows: for 0.1–9 years of smoking (white bars), $P = 0.35$; for 10–19 years of smoking (light gray bars), $P = 0.72$; for 20–29 years of smoking (dark gray bars), $P = 0.58$; and for ≥30 years of smoking (black bars), $P = 0.27$. *P* values for linear trend across duration of smoking within each intensity category were as follows: for 0.1–9 cigarettes/day, $P = 0.04$; for 10–19 cigarettes/day, $P = 0.03$; and for ≥20 cigarettes/day, $P = 0.03$.

and end of each smoking period during life, and the amount of tobacco smoked per day. The participants were also asked about their intakes of caffeine-containing coffee (cups/day), tea (cups/day), and cola (33 mL/day) and consumption of beer, wine, and liquor (units/week) throughout their lives and up to date of interview, with their age at start and end of each period with that habit. Never smokers were defined as people who had smoked fewer than 1 cigarette (or the equivalent amount of tobacco) per week for less than 6 months. Caffeine abstainers were defined as people who had drunk less than 1 cup of caffeine-containing coffee or tea or 1 cola per week for less than 1 year, and alcohol abstainers were defined as people who had drunk less than 1 unit of wine, beer, or liquor per week for less than 1 year. A positive family history of PD was defined as having at least 1 first-degree relative (parent or sibling) with PD.

The date of occurrence of the first cardinal symptom as stated in the medical records was used as the closing date for calculating cumulative consumption; controls were assigned the equivalent date of their respective case.

The study protocol was approved by the Danish Data Protection Agency (No. 2011-41-7025) and by the University of California, Los Angeles institutional review board for human subjects. All participants provided written informed consent.

Statistical analysis

To evaluate the associations of lifestyle habits and/or a family history of PD with the risk of IPD, we calculated odds ratios and 95% confidence intervals using unconditional and conditional logistic regression models. Because most of the patients had their medical record reviewed after the interview, the exclusion of patients who did not have IPD led to an excess number of controls. Thus, to increase the number of subjects included in the analyses, we chose unconditional regression as our primary model.

Analyses of cigarette smoking (ever having smoked; numbers of years of smoking; average number of cigarettes smoked per day; number of pack-years of smoking; and, for past smokers, age at cessation) were conducted with a time between smoking cessation and date of first cardinal symptom of 0 years and of 10 years; individuals who reported never having smoked were the reference group. Primary analyses of smoking were adjusted for sex and year of birth (continuous). Secondary analyses were further adjusted for highest attained educational level (basic, 7–12 years; vocational, 10–12 years; or higher, ≥13 years), caffeine intake (continuous), alcohol consumption (continuous), family history of PD (none, suspected, or confirmed) and degree of urbanization at residence (capital area, provincial city, rural area, peripheral region, of living abroad). Age is an important predictor of IPD and might be related to lifestyle habits; therefore, we also adjusted the secondary analyses for age at first cardinal symptom (continuous) to take into account the large age range for the onset of the cardinal symptoms (Table 1). For the cumulative measures, we used the Wald statistic to test for linear trends using the continuous values. A 2-sided 5% significance level was used for all statistical inferences. We also conducted an analysis that included both number of years of smoking and number of cigarettes smoked per day simultaneously in the regression model to examine the influence of frequency and intensity of smoking on the risk of IPD. We performed analyses stratified by the number of years between the index date and the date of interview (<5 vs. ≥5) in order to examine the associations of PD with the amount of time elapsed between the 2 events.

Among study participants for whom we had information on lifelong caffeine intake and alcohol consumption, we conducted separate analyses of caffeine intake divided into 5 categories (0–1, 1.1–3, 3.1–5, 5.1–7, and >7 cups/day), alcohol consumption divided into 5 categories (abstainers and 0–3, 3.1–7, 7.1–14, and >14 units/week), type of alcohol consumed (beer, wine, or liquor) in 3 categories (abstainers and 0.1–7 or >7 units/week), and history of PD in first-degree family members (no vs. yes). The analyses were conducted with 0 and 10 years of lag time between the intake and first cardinal symptom. We also conducted joint analyses of smoking and caffeine intake and of smoking and alcohol consumption to evaluate the combined associations of these factors with IPD. Likewise, we investigated the combined association of family history of PD and smoking habits with IPD. Separate composite exposure variables were created for smoking combined with caffeine, alcohol, and family history, and the combinations were included in the model as a factored set of terms (24). Statistical significance of the interaction term was evaluated after adding a multiplicative term of 2 exposures into the regression models. Data were analyzed using SAS statistical software, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Table 1 shows the characteristics of the patients and their matched population controls. The associations of cigarette

Table 3. Odds Ratios for Idiopathic Parkinson Disease by Daily Caffeine Intake, Weekly Alcohol Consumption, and Family History of Parkinson Disease, Denmark, 2008–2010

Habit or Characteristic	At Date of First Cardinal Symptom ($n = 2{,}990$[a])						10 Years Before First Cardinal Symptom ($n = 2{,}576$[a])					
	No. of Patients	No. of Controls	Primary Adjusted Analyses[b]		Secondary Adjusted Analyses		No. of Patients	No. of Controls	Primary Adjusted Analyses[b]		Secondary Adjusted Analyses	
			OR	95% CI	OR	95% CI			OR	95% CI	OR	95% CI
Caffeinated beverages, cups/day[c]												
0–1	163	88	1.00	Referent	1.00	Referent	154	83	1.00	Referent	1.00	Referent
1.1–3	412	325	0.68	0.50, 0.91	0.70	0.52, 0.95	401	289	0.74	0.54, 1.00	0.75	0.55, 1.03
3.1–5	394	482	0.44	0.33, 0.59	0.45	0.34, 0.62	356	417	0.45	0.33, 0.61	0.46	0.34, 0.63
5.1–7	245	339	0.38	0.28, 0.52	0.42	0.31, 0.58	201	262	0.40	0.29, 0.56	0.41	0.30, 0.58
>7	234	308	0.40	0.29, 0.55	0.44	0.32, 0.61	186	227	0.43	0.31, 0.60	0.42	0.30, 0.59
P for trend[d]				<0.001		<0.001				<0.001		<0.001
Alcohol, units/week[e]												
Abstainers	576	473	1.00	Referent	1.00	Referent	571	447	1.00	Referent	1.00	Referent
0.1–3	214	232	0.75	0.60, 0.93	0.78	0.62, 0.98	221	218	0.78	0.62, 0.97	0.79	0.62, 1.00
3.1–7	241	319	0.60	0.49, 0.75	0.63	0.51, 0.79	191	251	0.58	0.46, 0.73	0.62	0.49, 0.79
7.1–14	235	296	0.64	0.51, 0.79	0.68	0.54, 0.86	173	199	0.65	0.51, 0.84	0.66	0.51, 0.86
>14	182	222	0.65	0.51, 0.83	0.72	0.56, 0.93	142	163	0.65	0.50, 0.85	0.68	0.51, 0.90
P for trend[d]				0.96		0.44				0.93		0.96
Beer, units/week[f]												
Abstainers	576	473	1.00	Referent	1.00	Referent	571	447	1.00	Referent	1.00	Referent
0.1–7	447	544	0.64	0.53, 0.78	0.69	0.53, 0.91	387	464	0.62	0.51, 0.76	0.68	0.52, 0.88
>7	95	127	0.57	0.42, 0.78	0.63	0.43, 0.91	93	118	0.57	0.41, 0.79	0.57	0.40, 0.83
P for trend[d]				0.097		0.26				0.10		0.11
Wine, units/week[g]												
Abstainers	576	473	1.00	Referent	1.00	Referent	571	447	1.00	Referent	1.00	Referent
0.1–7	490	569	0.69	0.58, 0.82	0.78	0.62, 0.97	364	413	0.66	0.55, 0.80	0.81	0.63, 1.04
>7	197	232	0.67	0.53, 0.85	0.76	0.58, 1.00	139	155	0.67	0.51, 0.87	0.81	0.59, 1.12
P for trend[d]				0.64		0.42				0.73		0.62
Liquor, units/week[h]												
Abstainers	576	473	1.00	Referent	1.00	Referent	571	447	1.00	Referent	1.00	Referent
0.1–7	209	262	0.64	0.51, 0.81	0.82	0.50, 1.34	152	198	0.58	0.45, 0.75	0.57	0.32, 1.00
>7	19	21	0.71	0.37, 1.35	1.04	0.47, 2.31	16	14	0.84	0.40, 1.76	0.87	0.34, 2.21
P for trend[d]				0.34		0.33				0.30		0.25
Family history of PD[i]												
Negative	1,248	1,460	1.00	Referent	1.00	Referent						
Positive	200	82	2.84	2.17, 3,72	2.83	2.16, 3.72						

Abbreviations: CI, confidence interval; OR, odds ratio; PD, Parkinson disease.

[a] Study participants for whom information on lifelong caffeine intake and alcohol consumption was incomplete were excluded from analyses (0-years lag, $n = 694$; 10-year lag, $n = 1{,}108$).

[b] Adjusted for sex and year of birth.

[c] Adjusted for sex, year of birth, age at first cardinal symptom, highest attained educational level, pack-years of smoking, alcohol consumption, family history of PD, and level of urbanization.

[d] Linear trends were tested using the Wald test.

[e] Adjusted for sex, year of birth, age at first cardinal symptom, highest attained educational level, pack-years of smoking, caffeine intake, family history of PD, and level of urbanization.

[f] Adjusted for sex, year of birth, age at first cardinal symptom, highest attained educational level, pack-years of smoking, caffeine intake, wine consumption, liquor consumption, family history of PD, and level of urbanization.

[g] Adjusted for sex, year of birth, age at first cardinal symptom, highest attained educational level, pack-years of smoking, caffeine intake, beer consumption, liquor consumption, family history of PD, and level of urbanization.

[h] Adjusted for sex, year of birth, age at first cardinal symptom, highest attained educational level, pack-years of smoking, caffeine intake, beer consumption, wine consumption, family history of PD, and level of urbanization.

[i] Adjusted for sex, year of birth, age at first cardinal symptom, highest attained educational level, pack-years of smoking, caffeine intake, and level of urbanization.

Table 4. Odds Ratios for Idiopathic Parkinson Disease by Smoking Status Combined With Caffeine Intake and Alcohol Consumption, Denmark, 2008–2010

Intake	All Study Subjects ($n = 2,990$)							
	Never Smokers ($n = 1,297$)				Ever Smokers ($n = 1,693$)			
	No. of Patients	No. of Controls	Secondary Adjusted OR	95% CI	No. of Patients	No. of Controls	Secondary Adjusted OR	95% CI
Intake of caffeinated beverages, cups/day[a]								
Low (≤3)	334	183	1.00	Referent	241	230	0.60	0.46, 0.78
Medium (3.1–5.5)	226	208	0.60	0.46, 0.78	208	331	0.34	0.27, 0.45
High (>5.5)	172	174	0.54	0.40, 0.72	267	416	0.35	0.27, 0.44
P for interaction[b]				0.84				
Alcohol intake, units/week[c]								
Low (0)	345	212	1.00	Referent	231	261	0.56	0.43, 0.72
Medium (0.1–7)	240	208	0.70	0.54, 0.91	215	343	0.40	0.31–0.52
High (>7)	147	145	0.61	0.45, 0.82	270	373	0.44	0.34–0.57
P for interaction[b]				0.33				

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Adjusted for sex, year of birth, age at first cardinal symptom, highest attained educational level, alcohol consumption, family history of Parkinson disease, and level of urbanization.

[b] Test for statistical interaction in a multiplicative model.

[c] Adjusted for sex, year of birth, age at first cardinal symptom, highest attained educational level, caffeine intake, family history of Parkinson disease, and level of urbanization.

smoking at the date of first cardinal symptom and 10 years before with IPD are summarized in Table 2. In the analysis of subjects grouped by average number of cigarettes smoked per day, we observed a relatively uniform negative association of smoking with IPD, even among those who smoked 10 or fewer cigarettes per day. In the analysis in which we grouped subjects by years of smoking, however, we observed a steady decrease in risk for IPD with increasing length of exposure. Thus, current smokers who had smoked for 40 years or more had an odds ratio for IPD as low as 0.30 (95% confidence interval: 0.21, 0.44) (data not shown). Analyses stratified by sex yielded similar associations, although the odds ratios were slightly lower for men than for women (data not shown). In the analysis of subjects grouped by both duration of smoking and daily consumption of cigarettes, we observed a steady decrease in odds ratios for IPD with increasing number of years of smoking in all categories of number of cigarettes smoked per day, but there was no further strengthening of the association beyond consumption of 10 cigarettes per day in any of the duration categories (Figure 1). Stratification on time elapsed between index date and date of interview did not change the results to any appreciable extent, and we observed no notable difference in results when using conditional logistic regression models (data not shown).

Lifestyle habits, family history, and combined associations with smoking

Caffeine intake and alcohol consumption adjusted mutually for each other and for smoking was each inversely associated with IPD (Table 3). As was the case for smoking, the observed patterns indicated that a moderate daily intake of caffeine or alcohol was inversely associated with IPD, with no further contributions from a higher intake. Inverse associations were also observed when a lag time of 10 years was applied between intake and first cardinal symptom. When we examined type of alcohol, especially beer consumption appeared to contribute to the inverse association. In the analyses stratified by sex, the risk estimates for caffeine intake and alcohol consumption were lower in men than women, and inverse associations with the different types of alcohol consumption were observed only in men (Web Table 1). After adjustment for lifestyle factors, having at least 1 first-degree relative with PD was associated with a 2.8-times higher risk for IPD (Table 3).

When smoking status (never vs. ever) was combined with caffeine intake and alcohol consumption, higher intakes of caffeine and alcohol were inversely associated with IPD in both never and ever smokers (Table 4). The estimates for the combinations of smoking with medium or high intakes of caffeine or alcohol were, however, stronger than those for each lifestyle factor alone.

Table 5 shows that a positive family history of PD was associated with a 2.9-times higher risk of IPD, irrespective of smoking habits (never vs. ever); conversely, tobacco smoking was associated with an odds ratio of 0.55, irrespective of a family history of PD. In the joint analysis, we observed a modest increase in risk with both exposure conditions, that is, ever smokers with a family history of PD, when compared with never smokers with a negative family history of PD (Table 5).

Table 5. Odds Ratios for Idiopathic Parkinson Disease From Stratified and Joint Analyses of Smoking Status and Family History of Parkinson Disease, Denmark, 2008–2010

No. of Subjects	Smoking Status	Family History of PD	Primary Adjusted OR[a]	95% CI	Secondary Adjusted OR[b]	95% CI
			Positive Family History of PD			
1,576	Never	Positive	2.78	1.89, 4.07	2.90	1.96, 4.27
2,108	Ever	Positive	3.04	2.21, 4.19	2.94	2.13, 4.06
3,684	All	Positive	2.91	2.28, 3.71	2.83	2.16, 3.72
			Ever Smokers			
3,336	Ever	Negative	0.53	0.46, 0.61	0.55	0.47, 0.64
348	Ever	Positive	0.54	0.33, 0.90	0.55	0.32, 0.92
3,684	All	Ever	0.53	0.46, 0.61	0.55	0.48, 0.63
			Smoking and Family History of PD Combined			
1,414	Never	Negative	1.00	Referent	1.00	Referent
162	Never	Positive	2.62	1.74, 3.95	2.81	1.91, 4.13
1,922	Ever	Negative	0.55	0.47, 0.65	0.55	0.47, 0.63
186	Ever	Positive	1.67	1.16, 2.40	1.60	1.15, 2.23
P for interaction[c]			0.62		0.75	

Abbreviations: CI, confidence interval; OR, odds ratio; PD, Parkinson disease.

[a] Adjusted for sex and year of birth.

[b] Adjusted for sex, year of birth, age at first cardinal symptom, highest attained educational level, alcohol consumption, and level of urbanization.

[c] Test for statistical interaction in a multiplicative model.

DISCUSSION

In the present study of 1,808 patients with verified IDP, we found a strong inverse association between cigarette smoking and risk of IPD, even when smoking habits before the first cardinal symptom were lagged 10 years. Although we saw a downward trend with increasing number of years of smoking, there appeared to be no additional contribution from tobacco consumption of more than 10 cigarettes per day. In a large case-control study of the associations of both the duration and intensity of smoking with the risk of PD, Chen et al. (2) also found that duration was more important than intensity in modulating the smoking-PD relationship.

Although inconsistent results regarding the association between caffeine intake and risk of PD among women have been reported in previous studies (7–9, 25), we found that caffeine intake was associated with a lower risk of IPD in both men and women. The previous studies might have been limited by their lower average coffee consumption; intakes are comparatively high in Denmark. Inconsistent results were also obtained in previous studies of the risk of PD in relation to alcohol consumption (11–13, 26–31), but in a meta-analysis of 8 prospective studies and 24 case-control studies, Zhang et al. (14) reported an overall pooled relative risk for PD of 0.75 (95% confidence interval: 0.66, 0.85) among those with the highest alcohol consumption when compared with those with the lowest level. Further analyses showed that the inverse association was mostly driven by beer rather than by wine or liquor. In a prospective cohort study, Hernán et al. (12) also observed an inverse association between beer consumption and risk of PD, but only in men. In the present study, we found inverse associations with IPD for all types of alcohol in men. As in the case of smoking, we did not observe any strengthening of the inverse association with a consumption greater than a moderate intake, which again suggests that intensity is less important in mediating these lifestyle associations with IPD.

In our analysis of smoking in combination with caffeine consumption or alcohol consumption, we observed a stronger negative odds ratio for IPD in smokers with medium or high intakes of coffee or alcohol than for the individual lifestyle habits. To the best of our knowledge, the combined association of cigarette smoking and alcohol consumption with PD has not been reported before, although the joint associations of cigarette smoking and caffeine intake have been examined in a few studies (6, 9, 25). Whereas no clear interaction was observed in the study by Liu et al. (9), Powers et al. (25) reported findings similar to ours, that is, a lower risk for PD in subjects who used tobacco and had high intakes of caffeine than in subjects with only 1 of these habits.

Despite the abundance of literature inversely linking in particular tobacco smoking with the risk of PD, discussion continues about whether the decreased risk reflects a true association or a premorbid change in personality, with avoidance of addictive behavior, by people who later develop PD (32). Animal models of parkinsonism have demonstrated that both caffeine and nicotine can prevent neurotoxin-induced loss of neurons in the substantia nigra (33). Furthermore, because polyphenols in wine and ethanol have potent antioxidant effects (34) and nicotine and alcohol share nicotinic acetylcholine receptors as their biological target (35), it is conceivable that the negative associations observed in the present and

other studies represent causal inverse links between these lifestyle habits and IPD. Although we also observed inverse associations when lagging exposure 10 years from first cardinal symptom, reverse causality cannot be excluded if persons who later develop PD are less likely to engage in addictive behavior in the first place or if they quit much earlier.

Because there was a large number of IPD patients included in the present study, we were able to examine the joint associations of cigarette smoking and a family history of PD. The higher odds ratio associated with a family history of PD and the inverse association with tobacco smoking were essentially the same in analyses stratified by smoking habits and family history. Thus, although each single exposure was associated with a marked deviation in risk, when examining the variables in combination, we observed a more modest increase in the odds ratio of 1.6 comparing smokers with a family history of PD to never smokers without a family history. Studies of gene-environment interactions have shown that the inverse association between smoking and PD diminishes or is eliminated in people who carry risk alleles (36, 37), indicating that the smoking-IPD relationship is less strong in those at high risk because of a genetic predisposition. Joint exposure to tobacco smoking and a family history of PD was previously examined in only 1 case-control study of limited size (18). Somewhat surprisingly, Elbaz et al. (18) did not find an overall reduction in the risk of PD in smokers; however, they did find that people with a family history who had ever smoked had the highest risk of PD. After stratification by age, the finding was restricted to subjects older than 75 years of age. The latter finding was, however, based on only 6 PD patients and 1 control subject.

A major strength of our study is the systematic review of medical records undertaken to identify the subgroup of patients with IPD. Because an independent re-evaluation of a random sample of 50 medical records of patients initially considered to have IPD confirmed the diagnosis for 48 patients (96%), diagnostic misclassification was minimal (38). The present study was, however, limited by the fact that patients with less severe IPD were potentially excluded from our patient group because they were not registered with a diagnosis in the hospital registry.

Case-control studies are prone to recall bias because patients often search for explanations for their disease and are more likely to report exposures. In general, however, recall bias leads to overestimation of risks, because patients focus on potential risk factors for disease rather than protective aspects of lifestyle, which we examined in this study. It is therefore unlikely that the lower odds ratios associated with smoking, caffeine intake, and alcohol consumption observed in this study are a result of biased recall of exposures. Because our study population was elderly and we asked about habits over a lifetime, the reporting of exposures might have some inaccuracy. Nondifferential misclassification of exposure information might move odds ratio estimates toward the neutral value of 1, typically leading to underestimation of an increase or decrease. The information on PD among family members was also self-reported, and patients with PD have been found to report the occurrence of PD in first-degree relatives more often than control subjects (39). Nevertheless, the odds ratio for PD for subjects with a family history of PD was 2.8 in our study, which is compatible with the risk estimate of 2.9 reported in a recent meta-analysis (19).

The participation rate was high among the patients (81%) but moderate among controls (53%). Further examination of all eligible control subjects revealed that more nonparticipating controls died 1 year or less after contact for interview than those who participated (13.5% versus 5.9%). In addition, the nonparticipating controls were more often hospitalized for diseases related to tobacco smoking, such as ischemic heart disease or chronic obstructive pulmonary disease (19.3% versus 16.5%), indicating a slight underrepresentation of smokers among control subjects. Thus, although we cannot rule out the possibility of biased selection of study controls, the finding of a lower frequency of smoking-related disease among participating controls indicates that the observed decrease in risk for IPD associated with smoking in our study is slightly underestimated rather than exaggerated.

In conclusion, we found that duration of smoking, caffeine intake, and alcohol consumption seem to be more important than intensity of use as determinants of associations with IPD. When we combined information on smoking with that on caffeine and alcohol, the associations were stronger than among participants who reported just 1 of these exposures. Finally, compared with never smokers without a family history of PD, never smokers with a positive family history had the highest odds ratio for PD and smokers with a family history had a weaker association.

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