Movement Disorders
Vol. 23, No. 1, 2008, pp. 88-95

Combined Effects of Smoking, Coffee, and NSAIDs on Parkinson's Disease Risk

Karen M. Powers, BS,[1] Denise M. Kay, PhD,[2] Stewart A. Factor, DO,[3,4] Cyrus P. Zabetian MD, MS,[5,6] Donald S. Higgins, MD,[4] Ali Samii, MD,[6,7] John G. Nutt, MD,[8] Alida Griffith, MD,[9] Berta Leis, PhD,[9] John W. Roberts, MD,[10] Erica D. Martinez, BS,[5,6] Jennifer S. Montimurro, BS,[2] Harvey Checkoway, PhD,[1] and Haydeh Payami, PhD[2]*

[1]*Department of Environmental and Occupational Health Sciences, School of Public Health and Community Medicine, University of Washington, Seattle, Washington*
[2]*Genomics Institute, Wadsworth Center, New York State Department of Health, Albany, New York*
[3]*Department of Neurology, Emory University School of Medicine, Atlanta, Georgia*
[4]*Parkinson's Disease and Movement Disorder Center, Albany Medical Center, Albany, New York*
[5]*Geriatric Research Education and Clinical Center, VA Puget Sound Health Care System, Seattle, Washington*
[6]*Department of Neurology, University of Washington School of Medicine, Seattle, Washington*
[7]*Parkinson's Disease Research Education and Clinical Center, VA Puget Sound Health Care System, Seattle, Washington*
[8]*Department of Neurology, Oregon Health and Science University, Portland, Oregon*
[9]*Booth Gardner Parkinson's Care Center, Evergreen Hospital Medical Center, Kirkland, Washington*
[10]*Virginia Mason Medical Center, Seattle, Washington*

Abstract: Inverse associations of Parkinson's disease (PD) with cigarette smoking, coffee drinking, and nonsteroidal anti-inflammatory drug (NSAID) use have been reported individually, but their joint effects have not been examined. To quantify associations with PD for the individual, two-way and three-way combinations of these factors, a case–control association study with 1,186 PD patients and 928 controls was conducted. The study setting was the NeuroGenetics Research Consortium. Subjects completed a structured questionnaire regarding smoking, coffee, and NSAID consumption. Odds ratios were calculated using unconditional logistic regression. Smoking, coffee, and over the counter NSAID use as individual factors exhibited significantly reduced risks of 20% to 30%. The two-way and three-way combinations were associated with risk reduction of 37% to 49%, and 62%, respectively. Smoking and coffee exhibited significant inverse risk trends with increasing cumulative exposures, suggesting dose–response relations. With respect to the combination of all three exposures, persons who were at the highest exposure strata for smoking and coffee and used NSAIDs had an estimated 87% reduction in risk (OR = 0.13, 95% CI = 0.06–0.29). Whether this finding reflects true biologic protection needs to be investigated. © 2007 Movement Disorder Society

Key words: Parkinson's disease; smoking; coffee; NSAIDs; nonsteroidal anti-inflammatory drugs

Reduced Parkinson's disease (PD) risk among cigarette smokers, with strong evidence for inverse dose–response gradients, has been demonstrated consistently.[1] Inverse associations with PD risk have also been observed for caffeine intake, albeit not as consistently as with smoking.[1-4] Results of associations for nonsteroidal anti-inflammatory drugs (NSAIDs) and PD have been mixed, with some studies suggesting a reduced risk and others finding no association.[5-8] The combined effects of smoking, coffee drinking and NSAIDs have not been reported previously. Here we present findings from a case–control study on the individual and combined effects of smoking, coffee, and NSAIDs on PD risk.

*Correspondence to: Haydeh Payami, Genomics Institute, Wadsworth Center, New York State Department of Health, PO Box 22002 Albany, NY 12201-2002. E-mail: hpayami@wadsworth.org

Received 14 June 2007; Revised 18 September 2007; Accepted 21 September 2007

Published online 6 November 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21782

SUBJECTS AND METHODS

Subjects

Patients (n = 1,186) and controls (n = 928) were recruited through the movement disorder clinics of NeuroGenetics Research Consortium (NGRC). Informed consent approved by the Institutional Review Board of each participating institution was obtained from all subjects prior to enrollment. Uniform and standardized methods were used across all sites for diagnosis, subject selection (exclusion/inclusion criteria for cases and controls), and data acquisition. All patients were diagnosed by a movement disorder neurologist and met standard clinical diagnostic criteria for PD.[9] Patients were enrolled sequentially, regardless of age at disease onset or a family history of PD, and were unrelated to one another. Age at onset was defined as the age when the first symptom of PD was noticed (tremor, rigidity, or bradykinesia).[10,11] Family history was collected using a standardized questionnaire. Family history was considered positive if patient had one or more first- or second-degree relatives with PD. Controls were free of neurodegenerative disease by self-report, and included 450 spouses of PD patients, 27 spouses of patients with other neurodegenerative disorders, 353 community volunteers, and 98 unaffected blood relatives of PD patients. Community volunteers were recruited via advertisement and outreach programs, and included acquaintances of patients, volunteers from religious and civil organizations, and employees of the institutions where research was being conducted. Data were analyzed with and without the blood relatives; results did not differ.

NGRC began as a genetic study of PD in 1996 in Oregon and was expanded to Washington in 2002, to New York in 2004, and to Georgia in 2005. Exposure data collection was implemented in 2004 as a required data element for inclusion. Approximately 85% of patients and 85% of controls who were invited to participate in the study consented, and nearly 100% of those enrolled after 2004 provided exposure data. At the time of this study, NGRC had enrolled 1,762 PD patients and 2,064 controls,[12] but the present study used the subset, 1,186 patients and 928 controls, which had exposure data. To determine whether the exclusions of subjects with missing data biased the sample, we compared the present sample to those that were excluded, comparing patients to patients and controls to controls, for the following key variables: sex, age at onset, family history, genotypes for *SNCA* REP1 and *MAPT* H1H2 which are associated with PD risk,[12-14] data collection site (the four states), and age at blood draw. There was no significant difference between the excluded and included subjects in any of the variables except, as expected, for data collection site (most Oregon subjects were enrolled prior to 2004 without exposure data) and age at blood draw for controls (because excluded controls from Oregon were older). The characteristics of the overall NGRC data set is published.[12,15] Characteristics of the subjects included in this study are shown in Table 1.

Environmental Exposure Questionnaire

Exposure data were collected using a standardized, self-administered questionnaire. Detailed questions were asked regarding start and stop age of smoking, and multiple options were presented allowing for variable dose and durations smoked over time. Coffee drinking questions were asked in a similar format. A list of over the counter (OTC) and prescription (Rx) NSAIDs were presented to the subjects, emphasizing exclusion of aspirin and acetaminophen. If a person was a user of NSAIDs, then the amount and duration of both OTC and Rx NSAIDs were asked. NSAIDs are often used only as needed and cannot be defined with a single start or stop age; consequently, start and stop ages were not obtained.

TABLE 1. *Demographic characteristics of Parkinson's disease cases and controls*

	Overall		New York		Oregon		Washington		Georgia	
Characteristics	Cases (n = 1186)	Controls (n = 928)	Cases (n = 304)	Controls (n = 265)	Cases (n = 210)	Controls (n = 228)	Cases (n = 538)	Controls (n = 356)	Cases (n = 134)	Controls (n = 79)
Gender (% men)	66.6	40.3	62.2	37.4	60.5	41.2	72.3	44.4	63.4	29.1
Age at interview (median)	69.6 (30–97)[a]	67.7 (25–94)	70.6 (40–95)	66.2 (34–94)	73.1 (50–91)	68.5 (25–89)	68.0 (30–95)	69.0 (28–93)	67.7 (40–97)	68.0 (51–84)
Age at PD onset, (median)	59.0 (25–93)	—	62.0 (29–93)	—	57.5 (25–81)	—	58.0 (25–89)	—	59.0 (29–92)	—
Family history (% positive)[b]	23	—	16	—	37	—	20	—	27	—
Ethnicity (% Caucasian)	94.4	95.8	97.4	96.6	97.1	94.3	92.0	97.8	93.3	88.6

[a]Values in parentheses indicate ranges.
[b]Positive family history was defined as patient having at least one first- or second-degree relative with PD.

Data Analysis

Initial data analyses for individual exposures were performed by comparing never smokers to ever smokers (defined as having smoked at least 100 cigarettes in the lifetime); low vs. high coffee consumption (distinction made at the median for controls of the number of cups of coffee a subject consumed per day multiplied by the number of years that the subject drank coffee, which was 60 cups/day × years); and ever vs. never NSAIDs use (classified as OTC, Rx, or either). For the present analyses we chose to use high vs. low for coffee, instead of ever vs. never, because few people reported never having drunk coffee. Nevertheless, we present ever vs. never coffee estimates as well, so that the results can be directly compared to prior studies which used ever/never. The number of years since each person stopped smoking was estimated in addition to cumulative smoking, in pack-years, as a product of the packs per day and years smoked for each period. Cumulative exposure estimates were also calculated for coffee and NSAID use, measuring coffee-years as cups/day × years, and NSAID-years as times/day × years, respectively. Smoking was categorized into 0, >0 to 19, 20 to 39, and ≥40 pack-year strata. Control quartiles were used to determine the category boundaries for the four coffee and NSAIDs exposure-years strata. First, exposures were calculated and analyzed for subjects' entire lifetimes. Additionally, we truncated the smoking and coffee data at disease onset in an effort to avoid including exposures after the onset of PD. In order to apply the same relative exposure time for controls, we stratified PD cases by age into 5-year intervals, and used the mean onset age for each interval as the reference date at which to truncate exposures in controls of similar age. Start and end age for NSAID use were not available; therefore, NSAID exposure could not be truncated. Stratified analyses were performed for men and women, state (New York, Oregon, Washington, Georgia), PD onset (early onset defined as ≤50 years, late onset as >50 years), and family history (presence or absence of PD in at least one first- or second-degree relative). Family history was only available for cases; therefore, all controls were used for comparison with cases either with or without a family history of PD.

For the estimate of joint effects, ever/never smoking, high/low coffee, and ever/never NSAID use were compared. Two and three-way interaction models were used to test for interactions [deviation from multiplicative model for odds ratio (OR)] between these three dichotomous exposures. We also determined the risk of PD for those NSAID users in the highest quartiles of smoking and coffee drinking relative to the lowest. NSAID dosage was not examined in joint effect analysis because it was not significant individually.

OR and 95% confidence intervals (CI) for each exposure were estimated using unconditional logistic regression adjusting for age, ethnicity (Caucasian vs. other), gender, and state. The crude and mutually adjusted ORs for smoking, coffee, and NSAIDs were similar; therefore, only adjusted results are shown. Grouped linear terms, with categories assigned scores of 0, 1, 2,. . . , were constructed and the Wald statistic was used as a test for linear trends. Data were analyzed with and without the blood relatives as controls, and the results did not differ. The joint effects were also analyzed with and without blood relatives and results were nearly identical. Therefore, the blood relatives were included in the analysis. Stratified analyses were performed for men and women, the four states, early and late onset PD, and familial and nonfamilial PD. Owing to larger sample size requirements for interaction studies, stratified analysis was performed only for gender in the two-way joint effects analysis. The number of subjects used in each analysis, as reported in Tables 2–5, differs because each section of the questionnaire (smoking, coffee, and NSAIDs) was evaluated independently for completeness and inclusion in the analysis; hence, a person may have contributed data to one exposure and not the other. Analysis was conducted using *SPSS statistical software version 12.0.1 2003* (Chicago, IL). Statistical significance was set at $P < 0.05$, two-tailed.

RESULTS

Smoking

Ever smoking was associated with 23% reduction in risk, and current smoking was associated with 55% reduction risk (Table 2). The inverse association showed a significant dose–response trend, where risk decreased with increasing smoking pack-years ($P < 0.001$). The lowest risk, reduced by 56%, was seen for the highest strata of ≥40 pack-years. Results were nearly identical when data were truncated at age at onset; for instance, the pack-year analysis truncated to PD onset revealed a significant inverse trend ($P < 0.001$) with OR = 0.43 (95% CI: 0.30, 0.63) for the highest strata of ≥40 pack-years.

Stratified analyses for men and women, the four states, early and late onset, and positive and negative family history yielded similar results. In every subanalysis (gender, state, onset, and family history), ever smoking was associated with reduced risk (OR = 0.88–0.56), risk decreased consistently as a function of increasing pack-years, and the lowest risk was seen at the highest strata of

TABLE 2. *Associations of Parkinson's disease with cigarette smoking*

Smoking status	Men and women				Men				Women			
	Cases	Controls	OR*	95% CI	Cases	Controls	OR*	95% CI	Cases	Controls	OR*	95% CI
Never smoked	656	481	1.0	Ref	393	152	1.0	Ref	263	329	1.0	Ref
Ever smoked[a]	530	447	0.77	0.64–0.93	397	222	0.76	0.59–0.99	133	225	0.81	0.61–1.07
Years since stopped smoking												
Never smoked	656	481	1.0	Ref	393	152	1.0	Ref	263	329	1.0	Ref
≥40	152	96	0.94	0.69–1.27	115	53	0.93	0.63–1.38	37	43	1.00	0.61–1.63
30–39	125	93	0.84	0.61–1.15	91	51	0.72	0.48–1.08	34	42	1.10	0.67–1.81
20–29	113	99	0.73	0.53–1.01	84	52	0.70	0.47–1.06	29	47	0.81	0.49–1.34
5–19	86	80	0.75	0.52–1.06	69	34	0.84	0.53–1.33	17	46	0.59	0.33–1.08
>1–4	15	13	0.82	0.37–1.82	11	5	0.95	0.31–2.88	4	8	0.70	0.21–2.35
≤1/Current smoker	37	66	0.45	0.29–0.70	25	27	0.43	0.23–0.79	12	39	0.46	0.23–0.92
Pack-years												
0	693	500	1.0	Ref	425	162	1.0	Ref	268	338	1.0	Ref
>0–19	324	239	0.89	0.72–1.11	221	102	0.83	0.61–1.12	103	137	1.01	0.74–1.38
20–39	88	83	0.62	0.44–0.88	75	48	0.67	0.44–1.03	13	35	0.52	0.26–1.03
≥40	72	97	0.44	0.31–0.64	64	59	0.49	0.32–0.74	8	38	0.31	0.14–0.69
P for trend				<0.001				0.001				0.004

*Odds ratio adjusted for age, ethnicity, coffee, NSAIDs, and state (and gender for men and women combined)

[a]Includes those who said yes to ever smoking but did not indicate how long. The numbers of subjects used in never/ever calculation are not identical to the numbers used in pack-years calculations, because the former included every subject who answered the yes/no question on smoking, even if they did not answer dosage and duration questions, whereas the latter required that subjects answered additional questions on dose and duration. The numbers classified as never smoked (656) is less than the numbers of individuals classified as 0 pack-years (693) because 57 individuals reported having smoked >100 cigarettes but checked zero pack-years because they never smoked on a continuous basis.

≥40 pack-years for men (OR = 0.49, 95% CI: 0.32–0.74), women (OR = 0.31, 95% CI: 0.14–0.69); New York (OR = 0.50, 95% CI: 0.26–0.97), Oregon (OR = 0.26, 95% CI: 0.11–0.62), Washington (OR = 0.48, 95% CI: 0.28–0.84), Georgia (OR = 0.46, 95% CI: 0.10–2.08); early onset PD (OR = 0.53, 95% CI: 0.23–1.24), late onset PD (OR = 0.41, 95% CI: 0.27–0.62), positive family history (OR = 0.44, 95% CI: 0.24–0.80), and negative family history (OR = 0.46, 95% CI: 0.31–0.67).

Coffee

High coffee consumption was associated with 25% risk reduction (Table 3). (When coffee drinking was stratified as ever vs. never for comparability to some literature, OR = 0.81, 95% CI: 0.62–1.06). A significant inverse dose–response gradient was present ($P < 0.001$), where the highest vs. the lowest quartile was associated with 43% risk reduction (Table 3). Re-analysis with data truncated to PD onset produced similar results, where the highest coffee consumption stratum was associated with 45% lower risk than the lowest stratum (OR = 0.55, 95% CI: 0.41–0.74). The coffee effect was more pronounced in men than in women, and the coffee dose–response trend was highly significant in men but not in women (Table 3). Stratified analyses yielded similar results for lifetime or truncated data: comparing highest to lowest coffee consumption quartiles, risk was reduced for early

TABLE 3. *Associations of Parkinson's disease with coffee drinking*

Coffee drinking	Men and Women				Men				Women			
	Cases	Controls	OR*	95% CI	Cases	Controls	OR*	95% CI	Cases	Controls	OR*	95% CI
Coffee-yrs[a]												
Low 0–59	714	499	1.0	Ref	458	172	1.0	Ref	256	327	1.0	Ref
High ≥60	463	420	0.75	0.62–0.91	327	199	0.70	0.54–0.91	136	221	0.83	0.62–1.10
Coffee-yrs												
0–14	402	286	1.0	Ref	252	97	1.0	Ref	150	189	1.0	Ref
15–59	312	213	1.05	0.82–1.34	206	75	1.06	0.74–1.52	106	138	1.07	0.76–1.50
60–119	283	206	095	0.74–1.23	190	91	0.86	0.61–1.23	93	115	1.09	0.76–1.57
≥120	180	214	0.57	0.43–0.75	137	108	0.57	0.40–0.82	43	106	0.58	0.38–0.89
P for trend				<0.001				0.003				0.078

*Odds ratio adjusted for smoking, NSAIDs, age, ethnicity, and state (and gender for men and women combined).

[a]Coffee cups/day × years.

onset PD (OR = 0.45, 95% CI: 0.24–0.87), late onset PD (OR = 0.61, 95% CI: 0.44–0.83), subjects with positive family history (OR = 0.52, 95% CI: 0.34–0.81), subjects with negative family history (OR = 0.60, 95% CI: 0.44–0.80), in Oregon (OR = 0.50, 95% CI: 0.28–0.90), Washington (OR = 0.61, 95% CI: 0.39–0.93), New York (OR = 0.49, 95% CI: 0.28–0.88), but not Georgia (OR = 0.94, 95% CI: 0.38–2.29).

NSAIDs

The use of OTC NSAIDs was associated with a 19% risk reduction, but no dose–response trend was detected (Table 4). Rx NSAID use was not significantly related to PD risk in any of the analyses. Stratified analysis by gender showed a more prominent OTC NSAIDs effect in women than in men (Table 4). The results among the four states were inconsistent. Significantly reduced risks for having ever used NSAIDs (OTC or Rx) were observed for Oregon (OR = 0.64, 95% CI: 0.41–0.99) and Washington (OR = 0.60, 95% CI: 0.43–0.84), but not for New York (OR = 1.39, 95% CI: 0.95–2.03) or Georgia (OR = 1.06, 95% CI: 0.52–2.18). The analysis stratified by age at onset yielded a similar risk reduction of about 20% for users of OTC NSAIDs for both early and late onset PD, but they were not statistically significant. Stratified analysis by family history revealed PD risk reduction from ever any NSAID use in nonfamilial PD (OR = 0.79, 95% CI: 0.63–0.98) but not in familial PD (OR = 1.06, 95% CI: 0.77–1.47).

Joint Effects

Effects of smoking, coffee, and NSAIDs appeared to be independent and cumulative. Interaction models between each of the two-way combinations did not yield significant results, indicating lack of significant deviation from a multiplicative mathematical model for the OR. The combinations of any two factors resulted in lower risks than the risks associated with the individual factors (Table 5A). Even lower risks were seen with the combination of all three exposures (Table 5B). Subjects who smoked, drank high level of coffee, and used NSAIDs had 62% lower risk than subjects who did not smoke, drank little coffee, and used no NSAIDs (Table 5B). A similar result was obtained when controls who were related to patients were excluded (OR = 0.40, 95% CI: 0.28–0.59). The lowest risk was observed when the highest strata of smoking and coffee drinking, and ever NSAID use was compared to nonsmoking, lowest-coffee drinking, and no NSAID use (OR = 0.13, 95% CI: 0.06–0.29, Table 5C). Again, results were the same when relatives were excluded (OR = 0.13, 95% CI: 0.06–0.29).

TABLE 4. *Associations of Parkinson's disease with NSAID use*

	Men and Women				Men				Women			
NSAID use	Cases	Controls	OR*	95% CI	Cases	Controls	OR*	95% CI	Cases	Controls	OR*	95% CI
OTC												
Never	483	310	1.0	Ref	334	153	1.0	Ref	149	157	1.0	Ref
Ever[a]	677	597	0.81	0.67–0.98	439	215	0.87	0.66–1.13	238	382	0.73	0.55–0.98
NSAID-years[b]												
0	543	359	1.0	Ref	374	173	1.0	Ref	169	186	1.0	Ref
>0–1.4	198	177	0.80	0.62–1.04	125	66	0.82	0.57–1.18	73	111	0.76	0.53–1.11
1.5–3.0	190	193	0.75	0.58–0.97	122	68	0.79	0.55–1.13	68	125	0.69	0.47–1.01
>3	214	169	0.98	0.75–1.27	140	56	1.09	0.75–1.59	74	113	0.87	0.59–1.27
P for trend				0.387				0.908				0.244
Rx												
Never	782	572	1.0	Ref	542	255	1.0	Ref	240	317	1.0	Ref
Ever[a]	368	321	0.92	0.76–1.13	225	103	0.99	0.75–1.32	143	218	0.87	0.66–1.14
NSAID-years[b]												
0	805	590	1.0	Ref	560	260	1.0	Ref	245	330	1.0	Ref
>0–0.29	110	102	0.92	0.68–1.25	61	33	0.88	0.55–1.40	49	69	0.99	0.65–1.49
0.3–2.0	108	88	0.99	0.72–1.36	67	27	1.10	0.68–1.77	41	61	0.89	0.58–1.39
>2	122	106	0.97	0.72–1.30	74	34	0.97	0.62–1.51	48	72	0.96	0.63–1.44
P for trend				0.787				0.985				0.695
OTC or Rx												
Never	408	256	1.0	Ref	289	131	1.0	Ref	119	125	1.0	Ref
Ever[a]	769	663	0.83	0.68–1.02	496	240	0.88	0.67–1.15	273	423	0.77	0.56–1.04

*Odds ratio adjusted for smoking, coffee, age, ethnicity,and state (and gender for men and women combined)
[a]Includes those who said yes to NSAIDs but did not indicate how long.
[b]NSAID times/day × years.

TABLE 5. *Joint effects of smoking, coffee, and NSAIDs*

Exposure		Men and Women				Men				Women			
		Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
A. Two-way categorical comparisons[a]													
Smoking	Coffee												
No	Low	448	315	1.0	Ref	264	94	1.0	Ref	184	221	1.0	Ref
Yes	Low	266	183	0.85	0.66–1.09	194	77	0.87	0.61–1.24	72	106	0.82	0.57–1.18
No	High	207	166	0.80	0.62–1.05	128	58	0.76	0.52–1.13	79	108	0.82	0.57–1.17
Yes	High	254	254	0.51	0.40–0.65	197	141	0.49	0.35–0.67	57	113	0.59	0.40–0.86
Smoking	NSAIDs												
No	No	226	126	1.0	Ref	141	55	1.0	Ref	85	71	1.0	Ref
Yes	No	181	129	0.70	0.50–0.98	147	75	0.87	0.57–1.34	34	54	0.57	0.33–0.99
No	Yes	429	355	0.78	0.59–1.03	251	97	0.99	0.66–1.47	178	258	0.65	0.44–0.95
Yes	Yes	339	308	0.63	0.48–0.84	244	143	0.71	0.48–1.05	95	165	0.59	0.39–0.90
NSAIDs	Coffee												
No	Low	237	135	1.0	Ref	163	60	1.0	Ref	74	75	1.0	Ref
Yes	Low	477	363	0.88	0.67–1.15	295	111	0.93	0.63–1.35	182	252	0.85	0.58–1.26
No	High	170	120	0.82	0.59–1.14	125	70	0.74	0.48–1.14	45	50	1.03	0.61–1.75
Yes	High	291	300	0.63	0.47–0.84	200	129	0.61	0.42–0.90	91	171	0.65	0.43–1.00

	Smoking	Coffee	NSAIDs	Cases	Controls	OR	95% CI
B. Three-way categorical comparisons[a]							
− − −	No	Low	No	157	83	1.0	Ref
− − +	No	Low	Yes	291	232	0.76	0.54–1.06
− + −	No	High	No	69	43	0.77	0.47–1.25
− + +	No	High	Yes	138	123	0.62	0.43–0.91
+ − −	Yes	Low	No	80	52	0.63	0.39–0.99
+ − +	Yes	Low	Yes	186	131	0.73	0.50–1.05
+ + −	Yes	High	No	101	77	0.52	0.34–0.78
+ + +	Yes	High	Yes	153	177	0.38	0.27–0.55
C. Three-way dose trends[b]							
Lowest	No	Lowest	No	107	63	1.0	Ref
Middle	Any	Any	No/Yes	1057	822	0.74	0.53–1.04
Highest	Highest	Highest	Yes	11	33	0.13	0.06–0.29

P for trend < 0.001.

ORs were adjusted for age, ethnicity, and state; and for gender for men and women combined; and mutually adjusted for smoking, NSAIDs and coffee as appropriate

[a]Categories were defined as ever or never smoker (Yes, No), below or above median (60 cups/day × yrs) consumption of coffee (low, high); and ever or never use of OTC or Rx NSAID (Yes, No).

[b]For dose trends, the lowest dose group included subjects who did not smoke and drank the least coffee (lowest quartile of ≤14 cups/day × yrs) and never used NSAIDs. The highest dose group included subjects who smoked the heaviest (highest quartile of ≥40 pack-years), drank the most coffee (highest quartile of ≥120 cups/day × yrs) and used OTC or Rx NSAIDs (small sample size prevented using highest dose for NSAIDs). The middle group included all other subjects who did not qualify for the lowest or the highest strata.

DISCUSSION

Although smoking, coffee, and NSAIDs have been extensively studied individually, to our knowledge, there has been no previous study of the joint effects of these factors. Here, we confirmed previously observed individual effects, and showed that risk was further reduced when combinations were examined. Smoking and coffee drinking had the most significant effects, individually and in combination. NSAID results were equivocal when considered alone, and differed by family history and site, but they clearly showed an effect when examined in combination with smoking and coffee. The risk reduction displayed a dose–response pattern for smoking and coffee, but not for NSAIDs. Risk reduction was increased from 20% to 30% for individual effects to 37% to 49% for two-way joint effects, and to 62% for three-way combination. Considering dosage of coffee and smoking, risk was reduced by 87% in individuals who smoked the most heavily, drank the most coffee and used NSAIDs, as compared to those who did not smoke, drank the least coffee and did not use NSAIDs. These observational associations are not necessarily causal relationships.

The strength of our study was the simultaneous collection of data on different exposures on a large number of subjects, which made it possible to determine the joint effects. This was an exploratory study, and the results should be followed-up for confirmation in prospective studies. Our study was originally designed as a genetic study and exposure data collection was added at a later

date, thus the study design was not optimal for epidemiologic investigation. One limitation was the case–control nature of the study and dependence upon questionnaires, administered later in life, to elicit information regarding lifetime smoking habits, coffee drinking, and consumption of NSAIDs. Ideally, such studies should be performed prospectively. Another issue was the selection of controls and suboptimal matching to patients for epidemiologic studies. Spouses, for example, are considered a suitable control population for genetic studies, because they have similar habits and exposures as the patients, but this can create overmatching for study of exposures and could lead to underestimation of the individual exposure effects, as was the case here. Despite the case–control nature of the study and its associated limitations, our findings for individual risk factors were qualitatively consistent with those from prospective studies.[1,3,7] The risk reductions in our study were lower in magnitude than previously reported for the individual exposures, possibly due to use of spouses as controls. The meta-analysis by Hernan et al.[1] reported a pooled relative risk (RR) of 0.59 in ever vs. never smokers as compared to our OR of 0.77, and a pooled RR of 0.70 in ever vs. never coffee drinkers as compared to our OR of 0.81. Results for current smoking and years since quit smoking were also consistent with the literature.[16] A gender difference, as seen here, was noted previously in the association of coffee with PD.[3] This gender difference has been attributed to women who used postmenopausal hormone treatment.[17] We did not have hormone replacement therapy data to investigate this issue. The risk of PD with NSAID use found by others has been mixed ranging from RR = 0.55 to no association.[5-8] Our results were also equivocal for NSAIDs in that data from two states showed a significant inverse association, and two did not. Interestingly, NSAIDs results differed according to family history, suggesting an inverse association with nonfamilial PD but not with familial PD. To our knowledge, this is the first analysis of NSAID by family history, thus replication of this finding would be of interest.

The nature of these inverse associations is unknown; they may represent a true biologic protection, or may be secondary associations through, for example, personality traits. Both nicotine and cigarette smoke have been shown to exhibit neuroprotection against nigrostriatal degeneration in mice and primates.[18-20] Evidence from studies in animals also suggests that caffeine has neuroprotective properties.[21,22] The protection associated with NSAID use is assumed to come from the anti-inflammatory effect,[23] protecting neurons from glutamate-induced toxicity,[24] but has also been linked to the depression of prostaglandins.[24,25] Although the evidence for neuroprotective effects of these factors is strong, there may also be a common link between behavior and predisposition to PD. PD patients have been reported to display a decrease in novelty seeking behavior which may begin early in life.[26,27] Thus, this personality trait might influence long-term exposure to a number of neuroprotective factors in addition to smoking and caffeine, and to neurotoxic agents.

In summary, our study suggests that the inverse associations of smoking, coffee, and NSAIDs with PD risk are cumulative. Given that the combined effects are strong and highly significant, suggesting up to 87% risk reduction for PD, the findings warrant follow-up in additional epidemiologic and experimental studies. Whether these associations are due to a direct protective effect of these exposures will require resolution by functional studies in animal models.

Acknowledgments: Funding was provided by Grant Number R01NS036960 from the National Institute of Neurological Disorders and Stroke, K08-NS044138, AG 08017; a VA Merit Review Award, and a Michael J. Fox Foundation Edmond J Safra Global Genetics Consortia Grant. We thank the individuals who participated in this study. We also thank Galen Richards for assistance with data collection. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

REFERENCES

1. Hernan MA, Takkouche B, Caamano-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann Neurol 2002;52:276-284.
2. Checkoway H, Powers K, Smith-Weller T, Franklin GM, Longstreth WT, Jr, Swanson PD. Parkinson's disease risks associated with cigarette smoking, alcohol consumption, and caffeine intake. Am J Epidemiol 2002;155:732-738.
3. Ascherio A, Zhang SM, Hernan MA, et al. Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. Ann Neurol 2001;50:56-63.
4. Ross GW, Abbott RD, Petrovitch H, et al. Association of coffee and caffeine intake with the risk of Parkinson disease. JAMA 2000;283:2674-2679.
5. Chen H, Jacobs E, Schwarzschild MA, et al. Nonsteroidal antiinflammatory drug use and the risk for Parkinson's disease. Ann Neurol 2005;58:963-967.
6. Chen H, Zhang SM, Hernan MA, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. Arch Neurol 2003;60:1059-1064.
7. Hernan M, Logroscino G, Garcia Rodriguez L. Nonsteroidal anti-inflammatory drugs and the incidence of Parkinson's disease. Neurology 2006;11:1097-1099.
8. Ton TG, Heckbert SR, Longstreth WT, Jr, et al. Nonsteroidal anti-inflammatory drugs and risk of Parkinson's disease. Mov Disord 2006;21:964-969.
9. Gibb W, Lees A. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:745-752.
10. Richards M, Marder K, Cote L, Mayeux R. Reliability of symptoms onset assessment in Parkinson's disease. Mov Disord 1994; 9:340-342.

11. Reider CR, Halter CA, Castelluccio PF, Oakes D, Nichols WC, Foroud T. Reliability of reported age at onset for Parkinson's disease. Mov Disord 2003;18:275-279.
12. Zabetian CP, Hutter CM, Factor SA, et al. Association analysis of MAPT H1 haplotype and subhaplotypes in Parkinson's disease. Ann Neurol 2007;10.1002/ana.21157.
13. Maraganore DM, de Andrade M, Elbaz A, et al. Collaborative analysis of α-synuclein gene promoter variability and Parkinson disease. JAMA 2006;296:661-670.
14. Zhang J, Song Y, Chen H, Fan D. The tau gene haplotype h1 confers a susceptibility to Parkinson's disease. Eur Neurol 2005; 53:15-21.
15. Kay DM, Zabetian CP, Factor SA, et al. Parkinson's disease and LRRK2: frequency of a common mutation in U.S. movement disorder clinics. Mov Disord 2006;21:519-523.
16. Ritz B, Ascherio A, Checkoway H, et al. Pooled analysis of tobacco use and risk of Parkinson disease. Arch Neurol 2007;64: 990-997.
17. Ascherio A, Weisskopf MG, O'Reilly EJ, et al. Coffee consumption, gender, and Parkinson's disease mortality in the cancer prevention study II cohort: the modifying effects of estrogen. Am J Epidemiol 2004;160:977-984.
18. Parain K, Hapdey C, Rousselet E, Marchand V, Dumery B, Hirsch EC. Cigarette smoke and nicotine protect dopaminergic neurons against the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine Parkinsonian toxin. Brain Res 2003;984:224-232.
19. Quik M, Di Monte DA. Nicotine administration reduces striatal MPP+ levels in mice. Brain Res 2001;917:219-224.
20. Quik M, Parameswaran N, McCallum SE, et al. Chronic oral nicotine treatment protects against striatal degeneration in MPTP-treated primates. J Neurochem 2006;98:1866-1875.
21. Ross GW, Petrovitch H. Current evidence for neuroprotective effects of nicotine and caffeine against Parkinson's disease. Drugs Aging 2001;18:797-806.
22. Schwarzschild MA, Chen JF, Ascherio A. Caffeinated clues and the promise of adenosine A(2A) antagonists in PD. Neurology 2002;58:1154-1160.
23. Liu B, Gao HM, Hong JS. Parkinson's disease and exposure to infectious agents and pesticides and the occurrence of brain injuries: role of neuroinflammation. Environ Health Perspect 2003; 111:1065-1073.
24. Casper D, Yaparpalvi U, Rempel N, Werner P. Ibuprofen protects dopaminergic neurons against glutamate toxicity in vitro. Neurosci Lett 2000;289:201-204.
25. Carrasco E, Casper D, Werner P. Dopaminergic neurotoxicity by 6-OHDA and MPP+: differential requirement for neuronal cyclooxygenase activity. J Neurosci Res 2005;81:121-131.
26. Evans AH, Lawrence AD, Potts J, et al. Relationship between impulsive sensation seeking traits, smoking, alcohol and caffeine intake, and Parkinson's disease. J Neurol Neurosurg Psychiatry 2006;77:317-321.
27. Menza MA, Golbe LI, Cody RA, Forman NE. Dopamine-related personality traits in Parkinson's disease. Neurology 1993;43(3, Part 1):505-508.