

Smoking duration, intensity, and risk of Parkinson disease



H. Chen, MD, PhD
 X. Huang, MD, PhD
 X. Guo, MD, PhD
 R.B. Mailman, PhD
 Y. Park, ScD
 F. Kamel, PhD
 D.M. Umbach, PhD
 Q. Xu, MD, PhD
 A. Hollenbeck, PhD
 A. Schatzkin, MD, PhD
 A. Blair, PhD

Address correspondence and reprint requests to Dr. Honglei Chen, Epidemiology Branch, National Institute of Environmental Health Sciences, 111 T.W. Alexander Dr., PO Box 12233, Mail drop A3-05, Research Triangle Park, NC 27709
 chenh2@niehs.nih.gov

ABSTRACT

Objective: To evaluate the relative importance of smoking duration vs intensity in reducing the risk of Parkinson disease (PD).

Methods: The study included 305,468 participants of the NIH-AARP Diet and Health cohort, of whom 1,662 had a PD diagnosis after 1995. We estimated odds ratios (OR) and 95% confidence intervals from multivariate logistic regression models.

Results: Compared with never smokers, the multivariate ORs were 0.78 for past smokers and 0.56 for current smokers. Among past smokers, a monotonic trend toward lower PD risk was observed for all indicators of more smoking. Stratified analyses indicated that smoking duration was associated with lower PD risk within fixed intensities of smoking. For example, compared with never smokers, the ORs among past smokers who smoked >20 cigarettes/day were 0.96 for 1–9 years of smoking, 0.78 for 10–19 years, 0.64 for 20–29 years, and 0.59 for 30 years or more (p for trend = 0.001). In contrast, at fixed duration, the typical number of cigarettes smoked per day in general was not related to PD risk. Close examination of smoking behaviors in early life showed that patients with PD were less likely to be smokers at each age period, but if they smoked, they smoked similar numbers of cigarettes per day as individuals without PD.

Conclusions: This large study suggests that long-term smoking is more important than smoking intensity in the smoking–Parkinson disease relationship. *Neurology*® 2010;74:878–884

GLOSSARY

CI = confidence interval; DH = Diet and Health; OR = odds ratio; PD = Parkinson disease.

Despite the well-known adverse effects of cigarette smoking on health, epidemiologic studies consistently find lower risk of PD among smokers.¹ Recent evidence suggests this association is likely to be causal,^{2–4} yet the small sample sizes and limited data on smoking in prior studies have left many details of this relationship poorly understood. Of particular importance is the relative impact of duration vs intensity of smoking on PD risk. A thorough understanding of this relative impact is essential both for determining the clinical usefulness of administering the active constituents of tobacco to new patients with PD and for guiding animal experimental research.⁵ This is particularly true given the numerous adverse health effects of tobacco use. By taking advantage of the large NIH-AARP (formerly known as American Association of Retired Persons) Diet and Health (DH) Study,⁶ we examined detailed aspects of smoking over life in relation to PD, and report the greater importance of duration than intensity in mediating the smoking–PD relationship.

Editorial, page 870

Supplemental data at
www.neurology.org

e-Pub ahead of print on March 10, 2010, at www.neurology.org.

From the Epidemiology Branch (H.C., F.K., Q.X.) and Biostatistics Branch (D.M.U.), National Institute of Environmental Health Sciences, Research Triangle Park, NC; Departments of Neurology, Radiology, Neurosurgery, Pharmacology, Kinesiology & Bioengineering (X.H.), and Departments of Pharmacology and Neurology (R.B.M.), Pennsylvania State University–Milton S. Hershey Medical Center, Hershey; Westat Inc. (X.G.), Research Triangle Park, NC; Nutritional Epidemiology Branch (Y.P., A.S.) and Occupational and Environmental Epidemiology Branch (A.B.), National Cancer Institute, Rockville, MD; and AARP (A.H.), Washington, DC.

Study funding: Supported by the intramural research program of the NIH, the National Institute of Environmental Health Sciences (Z01-ES-101986), and the National Cancer Institute (Z01 CP010196-02).

Disclosure: Author disclosures are provided at the end of the article.

METHODS Study population and PD case identifica-

tion. The NIH-AARP DH cohort was assembled in 1995–1996 by the National Cancer Institute to investigate the roles of diet and lifestyle in cancer etiology.⁶ The cohort comprised 566,402 AARP members (ages 50–71) from 6 US states and 2 metropolitan areas who completed a comprehensive survey on diet and lifestyle.⁶ From 2004 to 2006, a follow-up survey was conducted among surviving participants to update lifestyle exposure and to ascertain the occurrence of major chronic diseases, including PD. A total of 318,261 participants (187,499 men and 130,762 women) responded to the follow-up survey and were thus eligible for the current study. The follow-up questionnaire asked participants whether they had been diagnosed by a doctor with PD and the year of diagnosis in the following categories: before 1985, 1985–1994, 1995–1999, or after 2000. A total of 2,432 participants reported a PD diagnosis on the follow-up questionnaire. As the baseline survey was in 1995–1996, we excluded from our analyses 459 cases who reported a PD diagnosis before 1995. We further excluded 293 self-reported cases whose diagnosis was later denied either by patients themselves or by their treating physicians in our diagnostic confirmation effort as described below and 18 cases who had missing information on smoking. Of those who did not report a PD diagnosis, we excluded 12,023 participants with missing data on smoking ($n = 4,053$) or PD status ($n = 7,970$). After these exclusions, we had a total of 1,662 self-reported PD cases diagnosed in or after 1995 and 303,806 participants without PD in the primary analyses.

As part of an effort to collect saliva samples from surviving patients with PD for genetic research, we began in 2007 to validate the self-reported PD diagnosis in this cohort. We asked surviving self-reported cases for permission to contact their treating neurologists, and then asked the neurologists either to complete a diagnostic questionnaire or to send us a copy of the patient's medical records. The questionnaire collects information on PD cardinal signs (rest tremor, rigidity, bradykinesia, and postural instability), response to dopaminergic treatments, and clinical features that may corroborate a PD diagnosis or suggest an alternative diagnosis. The medical records were reviewed and abstracted by a movement disorder specialist of the research team (X.H.). A case was confirmed if the diagnosis was considered clinically definitive or probable by the treating neurologist, or if the medical record included a final PD diagnosis or evidence of 2 or more cardinal signs with one being rest tremor or bradykinesia, a progressive course, responsiveness to dopaminergic treatments, and absence of features that suggest an alternative diagnosis. This protocol has been successfully implemented in other large cohorts.^{7,8} To date, we have received a total of 1,069 responses from physicians and 940 (87.9%) PD diagnoses were confirmed; 129 (12.1%) diagnoses were denied due to uncertainty ($n = 62$) or misdiagnosis ($n = 67$).

Exposure assessment. On the baseline questionnaire, we asked participants whether they had ever smoked more than 100 cigarettes during their lifetime. We asked ever smokers the typical number of cigarettes smoked per day and their current smoking status and asked former smokers the number of years since they last smoked. The follow-up questionnaire further ascertained the numbers of cigarettes smoked per day by 5-year age periods from <15 to 25–29 and then by 10-year age periods from 30–39 to 70 years or older. Using information from both the baseline and follow-up questionnaires, we reconstructed the following variables for our analyses: age at first smoking; age at last smoking; total years of smoking; typical number of cigarettes smoked per day; total pack-years of smoking; and, for past smok-

ers, years since last smoking. In addition to smoking, the baseline survey collected information on age, sex, and race as well as information on coffee and other caffeinated drinks as part of a food frequency questionnaire.⁶

Statistical analysis. We estimated odds ratios (OR) and 95% confidence intervals (CI) from unconditional logistic regression models. Lifetime smoking information was categorized in as much detail as sample sizes allowed: typical number of cigarettes smoked per day (1–10, 11–20, 21–30, 31–40, and >40), duration (years, 1–9, 10–19, 20–29, 30–39, and ≥ 40), pack-years (1–9, 10–19, 20–29, 30–39, 40–49, and ≥ 50), and years since last smoked (past smokers only, ≥ 35 , 30–34, 20–29, 10–19, 5–9, and 1–4). As almost all smokers (92.7%) started smoking in their late teens or early 20s and this cohort had a narrow age distribution, there was little variation in smoking duration among current smokers. Therefore, we limited analyses involving smoking duration to past smokers. Analyses were conducted first among all participants and then by gender, adjusting for age (in 5-year groups), race (non-Hispanic Caucasians vs others), caffeine intake (in quintiles), and gender (when appropriate). To evaluate the relative importance of duration vs intensity of smoking in past smokers, we included both variables simultaneously in the regression model. We also categorized past smokers according to combinations of years of smoking and number of cigarettes smoked per day to examine whether years of smoking was related to PD risk at fixed smoking intensities and vice versa. We tested the significance of linear trends by including the median of each exposure category as a continuous variable in the regression model.

To examine whether participants with and without PD had different smoking behavior in early life, we first calculated the proportion of smokers during each lifetime period up to age 50–59 according to whether they were diagnosed with PD after 1995. We then calculated the average number of cigarettes smoked per day at each age period for smokers with and without PD. Finally, we examined the average number of cigarettes smoked per day at each age period in relation to future PD risk, with and without adjusting for years of smoking. All statistical analyses were conducted using SAS software (Version 9.1, Cary, NC) and the significance tests were 2-tailed with $\alpha = 0.05$.

Standard protocol approvals, registrations, and patient consents. Participants consented to the study by returning survey questionnaires. The study protocol was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences and the Special Studies Institutional Review Board of the National Cancer Institute.

RESULTS Table 1 shows the population characteristics according to PD diagnosis after 1995. Compared with those without PD, PD cases were older at baseline, were more likely to be male, were less likely to be current smokers, and had less caffeine intake. Among ever smokers, more than 67.7% had tried cigarettes before age 20, and 92.7% had started smoking by age 25. The distribution of age at the initiation of smoking was similar between PD cases and noncases. Among past smokers, participants who later developed PD were more likely to quit at earlier ages than those who remained PD free: the proportions of quitters were 26.8% vs 24.0% before age 30,

Table 1 Population characteristics^a of the NIH-AARP Diet and Health Study with respect to Parkinson disease (PD) diagnosis after 1995

	Total		Men		Women	
	No PD (n = 303,806)	PD (n = 1,662)	No PD (n = 177,852)	PD (n = 1,228)	No PD (n = 125,954)	PD (n = 434)
Age, y	61.4 ± 5.3	63.8 ± 4.8	61.5 ± 5.3	64.0 ± 4.7	61.2 ± 5.4	63.3 ± 5.2
Men, %	58.5	73.9				
White, %	92.6	94.6	93.8	95.3	91.0	92.9
Caffeine intake, mg/d	234.0 (26.5-559.1)	187.7 (19.7-543.0)	265.3 (33.0-580.7)	212.2 (22.2-552.4)	210.3 (20.4-530.4)	120.8 (14.0-514.2)
Smokers, %						
Never	38.8	43.5	32.8	38.9	47.1	56.5
Past	51.4	51.3	58.8	57.1	41.0	34.8
Current	9.8	5.2	8.3	4.0	11.9	8.8

^aMeans ± SD are presented for age; medians and interquartile ranges (25%-75%) are presented for caffeine intake; and proportions are provided for other variables.

25.9% vs 24.9% before age 40, 21.7% vs 24.1% before age 50, and 25.6% vs 27.0% after age 50.

Compared with never smokers, the multivariate ORs were 0.78 for past smokers and 0.56 for baseline current smokers (table 2). Among past smokers, we observed a monotonic trend toward lower PD risk with more cigarettes smoked per day, longer years of smoking, fewer years since quitting, and more pack-years of smoking. In reference to never smokers, the multivariate ORs for the highest exposed category was 0.54 (p for trend < 0.0001) for years of smoking and 0.56 (p for trend < 0.0001) for years since last smoking as compared with 0.61 (p for trend = 0.01) for the number of cigarettes smoked per day.

When the model contained both duration and intensity simultaneously, the number of cigarettes smoked per day was no longer significantly associated with PD risk, whereas the risk estimates for years of smoking were barely changed. Compared with never smokers, the ORs were 0.94 for past smokers who smoked 1–10 cigarettes/day, 0.92 for 11–20 cigarettes/day, 0.94 for 21–30 cigarettes/day, 0.91 for 31–40 cigarettes/day, and 0.79 (95% CI 0.59–1.04) for >40 cigarettes/day (p for trend = 0.3). The ORs for years of smoking, on the other hand, were 0.94 for 1–9 years, 0.76 for 10–19 years, 0.74 for 20–29 years, 0.66 for 30–39 years, and 0.54 (95% CI 0.42–0.69) for ≥40 years (p for trend < 0.0001). We found similar patterns when we compared years since last smoking with typical number of cigarettes smoked per year (data not shown).

Current smokers represented only 9.8% of the study population at the baseline survey. Whereas current smokers at baseline had lower PD risk than never smokers, no further risk reduction was evident for more cigarettes smoked per day (table 2). The numbers of cases became too small to provide stable

estimates for current smokers with more than 30 cigarettes per day.

As expected, in both men and women, there were proportionally fewer smokers in each life period among individuals who later developed PD than among those who remained PD free (figure e-1 on the *Neurology*[®] Web site at www.neurology.org). On the other hand, there was little difference in the number of cigarettes smoked per day among smokers by later PD status (figure e-2). Starting from earlier 20s, being a smoker in each of the life periods was associated with a lower PD risk (table 3); however, those smoking more than 20 cigarettes per day did not have a lower risk of PD than participants smoking less. Further analyses suggested that these associations were largely explained by smoking duration (table 3).

Finally, we examined the joint associations of intensity and duration of smoking in relation to PD risk among past smokers (figure). In general, within each level of smoking intensity, longer duration tended to be associated with lower odds of having PD. Conversely, the typical number of cigarettes smoked per day was not related to the PD risk in most of the duration categories. We obtained similar results when we analyzed years since last smoking in conjunction with intensity (data not shown).

DISCUSSION Characterizing the smoking–PD relationship and understanding its nature are of great scientific and clinical importance, yet few epidemiologic studies have had large sample sizes and sufficient smoking information to do so. In the Cancer Prevention Study II Nutrition cohort, Thacker et al.⁹ indicated that the number of cigarettes per day, years of smoking, pack-years of smoking, and years since cessation were each associated with PD risk in a dose-response manner, consistent with results from a larger

Table 2 Odds ratios (OR) and 95% confidence intervals (CI) of Parkinson disease according to baseline smoking status^a

	All		Men		Women	
	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)
Never smokers	723/117,752	1.0	478/58,424	1.0	245/59,328	1.0
Past smokers	852/156,235	0.78 (0.70-0.86)	701/104,593	0.79 (0.70-0.89)	151/51,642	0.72 (0.59-0.88)
Cigarettes per day						
1-10	230/41,992	0.87 (0.75-1.01)	157/21,962	0.86 (0.71-1.03)	73/20,030	0.90 (0.69-1.17)
11-20	268/48,298	0.77 (0.67-0.89)	236/32,627	0.84 (0.71-0.98)	32/15,671	0.51 (0.35-0.73)
21-30	166/29,672	0.77 (0.65-0.91)	141/21,781	0.77 (0.64-0.93)	25/7,891	0.81 (0.53-1.22)
31-40	105/19,079	0.74 (0.60-0.91)	91/14,502	0.74 (0.59-0.93)	14/4,577	0.78 (0.45-1.34)
>40	75/15,965	0.61 (0.48-0.78)	72/12,943	0.66 (0.51-0.84)	3/3,022	0.26 (0.08-0.81)
p for trend		0.01		0.04		0.09
Years of smoking						
1-9	223/36,556	0.92 (0.79-1.07)	184/24,659	0.94 (0.79-1.12)	39/11,897	0.85 (0.60-1.20)
10-19	185/35,128	0.75 (0.63-0.88)	152/24,140	0.75 (0.62-0.90)	33/10,988	0.76 (0.53-1.10)
20-29	169/33,396	0.72 (0.61-0.85)	140/22,537	0.73 (0.61-0.89)	29/10,859	0.68 (0.46-1.00)
30-39	120/27,051	0.65 (0.53-0.79)	102/17,624	0.69 (0.56-0.86)	18/9,427	0.49 (0.30-0.79)
≥40	61/12,703	0.54 (0.41-0.70)	53/8,492	0.58 (0.43-0.77)	8/4,211	0.38 (0.19-0.77)
p for trend		<0.0001		<0.0001		0.004
Years since last smoking						
≥35	168/20,897	0.91 (0.77-1.09)	147/15,484	0.94 (0.78-1.13)	21/5,413	0.79 (0.50-1.25)
30-34	146/21,463	0.83 (0.69-1.00)	119/15,675	0.80 (0.65-0.98)	27/5,788	1.06 (0.71-1.58)
20-29	186/36,515	0.74 (0.63-0.87)	153/25,527	0.74 (0.61-0.89)	33/10,988	0.77 (0.53-1.10)
10-19	136/30,963	0.69 (0.57-0.83)	116/20,607	0.74 (0.60-0.91)	20/10,356	0.51 (0.32-0.81)
5-9	82/20,370	0.64 (0.51-0.81)	66/12,073	0.69 (0.53-0.90)	16/8,297	0.51 (0.30-0.84)
1-4	53/16,351	0.56 (0.42-0.74)	40/9,054	0.58 (0.42-0.81)	13/7,297	0.48 (0.28-0.85)
p for trend		<0.0001		0.006		0.005
Pack-years of smoking						
1-9	338/57,659	0.90 (0.79-1.02)	261/34,895	0.91 (0.79-1.06)	77/22,764	0.85 (0.66-1.10)
10-19	146/29,394	0.69 (0.58-0.83)	129/20,444	0.75 (0.61-0.91)	17/8,950	0.48 (0.29-0.79)
20-29	105/22,539	0.64 (0.52-0.79)	93/15,754	0.69 (0.55-0.86)	12/6,785	0.44 (0.25-0.79)
30-39	62/13,268	0.63 (0.48-0.81)	53/9,581	0.64 (0.48-0.85)	9/3,687	0.60 (0.31-1.17)
40-49	44/8,979	0.65 (0.48-0.88)	38/6,649	0.66 (0.47-0.91)	6/2,330	0.63 (0.28-1.41)
≥50	61/12,762	0.57 (0.44-0.74)	55/9,973	0.59 (0.44-0.78)	6/2,789	0.49 (0.22-1.11)
p for trend		<0.0001		<0.0001		0.04
Current smokers	87/29,819	0.56 (0.45-0.70)	49/14,835	0.47 (0.35-0.64)	38/14,984	0.74 (0.52-1.05)
Cigarettes per day						
1-10	24/7,964	0.58 (0.39-0.88)	11/3,276	0.45 (0.25-0.83)	13/4,688	0.78 (0.44-1.37)
11-20	35/11,997	0.57 (0.40-0.80)	19/5,558	0.48 (0.30-0.76)	16/6,439	0.72 (0.43-1.21)
>20	28/9,796	0.53 (0.36-0.78)	19/5,957	0.47 (0.30-0.76)	9/3,839	0.70 (0.35-1.37)
21-30	20/6,120	0.62 (0.39-0.97)	14/3,457	0.59 (0.35-1.02)	6/2,663	0.67 (0.29-1.51)
>30	8/3,676	0.40 (0.20-0.80)	5/2,500	0.30 (0.12-0.74)	3/1,176	0.77 (0.24-2.43)
p for trend		0.9		0.9		0.99

^aAdjusted for age, race, caffeine intake, and gender when appropriate.

Table 3 Odds ratios (OR) and 95% confidence intervals (CI) of Parkinson disease according to smoking intensity in each life period without and with adjustment for years of smoking

Age in years	Cases/controls ^a	Basic model ^b	Adjusting for years of smoking
<15			
No	1,371/252,261	1.0	1.0
<20 cigarettes/day	182/37,904	0.83 (0.71–0.97)	1.10 (0.92–1.30)
≥20 cigarettes/day	10/1,135	1.48 (0.79–2.76)	1.94 (1.03–3.64)
15–19			
No	1,006/174,506	1.0	1.0
<20 cigarettes/day	488/104,084	0.76 (0.68–0.84)	0.97 (0.84–1.13)
≥20 cigarettes/day	69/12,710	0.80 (0.62–1.02)	1.05 (0.80–1.37)
20–24			
No	806/132,820	1.0	1.0
<20 cigarettes/day	527/114,260	0.71 (0.63–0.79)	0.90 (0.71–1.15)
≥20 cigarettes/day	230/44,220	0.73 (0.63–0.85)	0.95 (0.73–1.24)
25–29			
No	833/137,346	1.0	1.0
<20 cigarettes/day	437/94,534	0.71 (0.64–0.80)	0.93 (0.74–1.18)
≥20 cigarettes/day	293/59,420	0.69 (0.60–0.79)	0.93 (0.72–1.20)
30–39			
No	929/154,237	1.0	1.0
<20 cigarettes/day	333/75,574	0.70 (0.62–0.79)	1.05 (0.81–1.36)
≥20 cigarettes/day	301/61,489	0.70 (0.62–0.80)	1.09 (0.83–1.43)
40–49			
No	1,110/188,092	1.0	1.0
<20 cigarettes/day	234/55,064	0.73 (0.63–0.84)	1.07 (0.85–1.33)
≥20 cigarettes/day	219/48,144	0.70 (0.61–0.81)	1.07 (0.84–1.36)
50–59			
No	1,329/231,748	1.0	1.0
<20 cigarettes/day	134/34,682	0.70 (0.59–0.84)	1.05 (0.80–1.36)
≥20 cigarettes/day	100/24,870	0.64 (0.52–0.79)	0.98 (0.73–1.32)

^aNumbers may not add up to total due to missing values.

^bAdjusted for age, gender, race, and caffeine intake.

pooled analysis of 11 US studies.¹⁰ Interestingly, both articles reported lower PD risk even among smokers who quit 2 decades before disease diagnosis. Further, in the Cancer Prevention Study II Nutrition cohort, the authors stated in the text that the association of PD with cigarettes per day lost its significance after adjusting for years of smoking, whereas the association between years of smoking and PD remained after adjusting for smoking intensity.

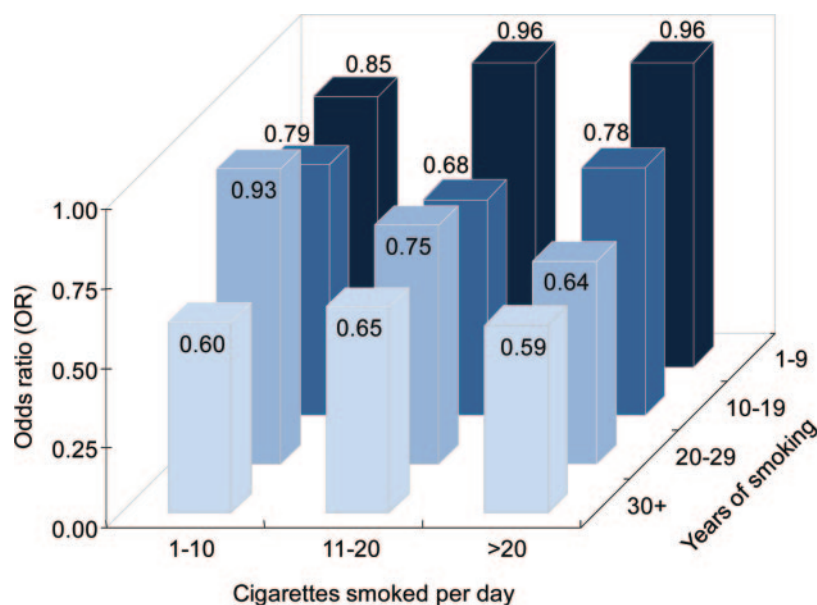
The large sample size and lifetime smoking data of the current study enabled us to examine the smoking–PD relationship in further detail. In addition to the significant dose-response relationships between various smoking indicators and PD risk, we showed that the duration and the recency of smoking were more important than smoking intensity in modulat-

ing PD risk. Among past smokers, the lowest risk of PD was observed for participants who smoked the longest or who had quit most recently. Further, the number of cigarettes smoked per day became irrelevant once adjusted for smoking duration or years since last smoking. Finally, a longer smoking duration or fewer years since quitting was generally associated with lower PD risk within strata of smoking intensity, whereas the reverse was not observed. Among current smokers, where there was little variation in smoking duration, the number of cigarettes smoked per day was not related to PD risk.

This study, consistent with previous ones,^{9,10} suggests that patients with PD were less likely than controls to develop habitual smoking in early life or they were able to quit earlier. Further, the overall epidemiologic evidence favors a causal relationship between smoking and PD over several alternatives. Suspicion that this association is related to higher mortality among PD smokers than PD nonsmokers cannot explain results from prospective cohorts,^{1,11,12} and previous studies found that PD smokers did not have a higher mortality than PD nonsmokers.^{13,14} Reverse causality also is an unlikely explanation because the current work, as well as 2 other recent studies,^{9,10} found lower PD risk even among smokers who had quit 2 decades ago. The other alternative hypothesis suggests that the association is explained either by confounding from common genetic factors or by a low novelty-seeking personality that underlies both avoidance of smoking and a higher PD risk. Genetic factors are unlikely to be a major confounder because smoking was associated with lower PD risk among genetically controlled twins.^{2,15} A link between a risk-adverse or low novelty-seeking personality and PD is primarily based on anecdotal clinical observations and case-control studies.^{16,17} Further, smoking was related to lower PD risk even after controlling for sensation-seeking score.¹⁸ Finally, recent findings on passive smoking,³ parental smoking,⁴ and secular changes in gender ratios on smoking and PD¹⁹ provide novel support for the hypothesis that smoking decreases PD risk.

The robust epidemiologic evidence on smoking and PD has led to experimental efforts to elucidate a biologic basis.²⁰ The existing animal models, however, may not be mechanistically similar, or at best, capture only a minor aspect of the smoking–PD relationship.⁵ This may explain why nicotine has been found to be protective in some animal experiments, but not in others.²⁰ Most animal PD models have focused on relatively short-term, high-dose protection against cellular damage from exogenous cytotoxicants. The acute pharmacologic effects of nicotine (e.g., effects on dopamine turnover or metabolism) make untangling experimental data diffi-

Figure Odds ratios of Parkinson disease according to joint categories of baseline years of smoking and cigarettes smoked per day among past smokers



Never smokers were used as the reference group. *p* for linear trend across years of smoking within fixed intensities: 0.3 (1-10 cigarettes/day), 0.04 (11-20 cigarette/day), 0.001 (>20 cigarette/day); *p* for linear trend across intensity of smoking within fixed duration groups: 0.4 (1-9 years), 0.8 (10-19 years), 0.06 (20-29 years), and 0.5 (\geq 30 years).

cult. Most importantly, results from the current study suggest a chronic long-term effect of tobacco chemicals that may saturate at a low daily dose. If this observation is confirmed, the high-dose, acute administration of tobacco chemicals in laboratory studies should possibly be eschewed for experiments based on low-dose and long-term administration.

These findings also have clinical implications as nicotine has been investigated as a neuroprotectant in clinical trials. Small trials using nicotine delivered via patch or chewing gum typically lasted from days to weeks and largely failed to show beneficial effects on PD.²¹⁻²⁵ The current study suggests that years of smoking (and hence nicotine administration) may be needed for any reduction of PD risk. Further, preliminary epidemiologic studies have shown that smoking was not associated with lower PD mortality^{13,14} or slower clinical progression.^{26,27} Therefore, while it is crucial to understand the smoking-Parkinson relationship, the epidemiologic evidence to date lends little support for the clinical usefulness of nicotine or other cigarette-derived chemicals in PD treatment.

The major limitation of this study is its reliance on self-report for case identification, inevitably leading to diagnostic and reporting errors. We tried to limit the potential impact from this source by excluding from the analysis erroneous reports identified in the ongoing validation study. Further, by contacting

patients' neurologists and conducting medical record review, we were able to confirm 88% of the cases whose medical information was available. Another limitation is that we did not have detailed information on the date at onset or date at diagnosis for all PD cases, and thus were unable to estimate the incidence of PD and to conduct time to event analysis. Further, measurement errors of exposure variables were also likely. It is possible that the years of smoking were more reliably recalled than smoking intensity, which might be partially responsible for our finding. The current analyses were limited to participants of the follow-up survey. Because preliminary epidemiologic data suggest that PD smokers and PD nonsmokers have a similar clinical course and mortality,^{13,14,26,27} this limitation was unlikely to introduce a substantial bias. Finally, to our knowledge, this is the first study that comprehensively examined the relative importance of smoking duration vs intensity in PD etiology; therefore, the validity and generalizability of this finding should be further examined in future investigations.

As nearly all smokers in this cohort started smoking in their late teens and early 20s, years of smoking and years since last smoking are highly correlated among past smokers. Therefore we were unable to rule out the possibility that our findings on years of smoking were actually due to years from cessation. For the same reason, we were unable to examine directly the potential effects of recent short-term high-dose smoking on PD among individuals who did not smoke in early life. Nonetheless, this large study showed that the duration of smoking was more important than its intensity in reducing PD risk. Although the numerous adverse health effects of cigarette smoking may eventually limit the clinical implications of the epidemiologic findings on smoking and PD, research to reveal the underlying chemicals and mechanisms are warranted.

ACKNOWLEDGMENT

The authors thank the participants of the NIH-AARP Diet and Health study for their contributions and Dr. Ross Ulmer from Westat Inc., Durham, NC, for statistical support.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Drs. Guo, Umbach, and Chen.

DISCLOSURE

Dr. Chen receives NIH intramural funding (Z01-ES-101986) and serves on the editorial board of the *International Journal of Molecular Epidemiology and Genetics*. Dr. Huang has served as a consultant for Easton Associate, Public Healthcare, Teva Pharmaceutical Industries Ltd., and the National Institute of Environmental Health Sciences; holds patent US 6,916,823 (issued 2005): Method of treatment of dopamine-related dysfunction (plus foreign patents) and has filed a patent regarding Early detection of Parkinson's disease using novel motor signs; has received honoraria for speaking and education activities not sponsored by industry; receives research support from the NIH/NINDS (NS060722 [PI]), the Pennsylvania Tobacco Settlement Fund and from Huck Institute of Penn State

University; and holds stock in BioValve Technologies, Inc. Dr. Guo reports no disclosures. Dr. Mailman serves on the editorial boards of the *Journal of Molecular and Biochemical Toxicology* and *Current Opinion in Central and Peripheral Nervous System (CPNS) Drugs*; receives royalties from the publication of *Introduction to Biochemical and Molecular Toxicology, 4th ed.* (Wiley, 2001); has received speaker honoraria from activities not sponsored by industry; serves as a consultant for Roche; receives research support from the NIH (U19 MH082441-01 [Penn State PI Project] and NS042402 [Co-PI]), the Pennsylvania Tobacco Settlement Fund, the Keystone Fund, and from the Commonwealth of Pennsylvania Ben Franklin Technology Development Authority; holds stock in Effipharma Inc. and BioValve Technologies, Inc.; has served as an expert witness in cases involving Eli Lilly and Company and Barr Laboratories, Inc.; holds the following patents (plus foreign patents on each): US 5,420,134 (issued 1995): Substituted hexahydrobenzo[a]phenanthridines; US 5,959,110 (issued 1999): Fused isoquinolines as dopamine receptor ligands; US 6,194,423 (issued 2001): Fused isoquinolines as dopamine receptor ligands; US 6,413,977 (issued 2002): Chromeno [4,3,2-DE]isoquinolines as potent dopamine receptor ligands; US 6,916,823 (issued 2005): Method of treatment of dopamine-related dysfunction; US 6,916,832 (issued 2005): Chromeno [4,3,2-DE] isoquinolines as potent dopamine receptor ligands; and has filed additional patent applications regarding: Dopamine agonists with improved pharmacokinetic properties, Method of administration of dopamine receptor agonists; and Co-administration of dopamine-receptor binding compounds. Dr. Park reports no disclosures. Dr. Kamel serves as an Associate Editor of *Environmental Health Perspectives* and on the editorial board of the *American Journal of Epidemiology*; and receives intramural research funding from the NIH/NIEHS. Dr. Umbach and Dr. Xu report no disclosures. Dr. Hollenbeck serves on the Scientific Advisory Committee of the Love/Avon Army of Women; and is a full-time salaried employee of AARP. Dr. Schatzkin is an employee of the NIH National Cancer Institute and serves as Principal Investigator of the NIH-AARP Diet and Health Study. Dr. Blair is a Scientist Emeritus at the National Cancer Institute and serves on the editorial advisory boards of the *Scandinavian Journal of Work Environment and Health*, the *American Journal of Industrial Medicine*, and the *Journal of Agricultural Safety and Health*. He also served as the Interim Director of the Occupational Cancer Research Centre in Toronto, ON, Canada.

Received August 1, 2009. Accepted in final form November 3, 2009.

REFERENCES

- 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.
- Tanner CM, Goldman SM, Aston DA, et al. Smoking and Parkinson's disease in twins. *Neurology* 2002;58:581–588.
- Mellick GD, Gartner CE, Silburn PA, Battistutta D. Passive smoking and Parkinson disease. *Neurology* 2006;67:179–180.
- O'Reilly EJ, Chen H, Gardener H, Gao X, Schwarzschild MA, Ascherio A. Smoking and Parkinson's disease: using parental smoking as a proxy to explore causality. *Am J Epidemiol* 2009;169:678–682.
- Quik M, O'Neill M, Perez XA. Nicotine neuroprotection against nigrostriatal damage: importance of the animal model. *Trends Pharmacol Sci* 2007;28:229–235.
- Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol* 2001;154:1119–1125.
- 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.
- Chen H, Zhang SM, Hernan MA, Willett WC, Ascherio A. Diet and Parkinson's disease: A potential role of dairy products in men. *Ann Neurol* 2002;52:793–801.
- Thacker EL, O'Reilly EJ, Weisskopf MG, et al. Temporal relationship between cigarette smoking and risk of Parkinson disease. *Neurology* 2007;68:764–768.
- Ritz B, Ascherio A, Checkoway H, et al. Pooled analysis of tobacco use and risk of Parkinson disease. *Arch Neurol* 2007;64:990–997.
- Hernan MA, Zhang SM, Rueda-deCastro AM, Colditz GA, Speizer FE, Ascherio A. Cigarette smoking and the incidence of Parkinson's disease in two prospective studies. *Ann Neurol* 2001;50:780–786.
- 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.
- Elbaz A, Bower JH, Peterson BJ, et al. Survival study of Parkinson disease in Olmsted County, Minnesota. *Arch Neurol* 2003;60:91–96.
- Chen H, Zhang SM, Schwarzschild MA, Hernán MA, Ascherio A. Survival of Parkinson's disease patients in a large prospective cohort of male health professionals. *Mov Disord* 2006;21:1002–1007.
- Wirdefeldt K, Gatz M, Pawitan Y, Pedersen NL. Risk and protective factors for Parkinson's disease: a study in Swedish twins. *Ann Neurol* 2005;57:27–33.
- Menza M. The personality associated with Parkinson's disease. *Curr Psychiatry Rep* 2000;2:421–426.
- Shihara LI, Brayne C. What is the evidence for a premorbid parkinsonian personality: a systematic review. *Mov Disord* 2006;21:1066–1072.
- 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.
- Morozova N, O'Reilly EJ, Ascherio A. Variations in gender ratios support the connection between smoking and Parkinson's disease. *Mov Disord* 2008;23:1414–1419.
- Quik M. Smoking, nicotine and Parkinson's disease. *Trends Neurosci* 2004;27:561–568.
- Vieregge A, Sieberer M, Jacobs H, Hagenah JM, Vieregge P. Transdermal nicotine in PD: a randomized, double-blind, placebo-controlled study. *Neurology* 2001;57:1032–1035.
- Lemay S, Chouinard S, Blanchet P, et al. Lack of efficacy of a nicotine transdermal treatment on motor and cognitive deficits in Parkinson's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2004;28:31–39.
- Ebersbach G, Stock M, Muller J, Wenning G, Wissel J, Poewe W. Worsening of motor performance in patients with Parkinson's disease following transdermal nicotine administration. *Mov Disord* 1999;14:1011–1013.
- Clemens P, Baron JA, Coffey D, Reeves A. The short-term effect of nicotine chewing gum in patients with Parkinson's disease. *Psychopharmacology* 1995;117:253–256.
- Villafane G, Cesaro P, Rialland A, et al. Chronic high dose transdermal nicotine in Parkinson's disease: an open trial. *Eur J Neurol* 2007;14:1313–1316.
- Alves G, Kurz M, Lie SA, Larsen JP. Cigarette smoking in Parkinson's disease: influence on disease progression. *Mov Disord* 2004;19:1087–1092.
- Kandinov B, Giladi N, Korczyn AD. The effect of cigarette smoking, tea, and coffee consumption on the progression of Parkinson's disease. *Parkinsonism Relat Disord* 2007;13:243–245.