Dietary nicotine intake and risk of Parkinson disease: a prospective study

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ABSTRACT

Background: Tobacco use was observed to be associated with a lower risk of Parkinson disease (PD) in previous epidemiologic studies, with nicotine as a potential candidate. The association between dietary nicotine and PD risk has, however, not been examined in prospective studies yet.

Objectives: We aimed to examine prospectively the association between dietary nicotine intake and subsequent PD risk among never-smokers.

Methods: The current study was based on never-smoker participants from 2 large prospective cohorts: the Nurses' Health Study (n = 31,615) and the Health Professionals Follow-up Study (n = 19,523). The studies contained information on dietary nicotine intake from 1986 from validated FFQs. Dietary nicotine intake was calculated based on consumption of peppers, tomatoes, processed tomatoes, potatoes, and tea. Incident cases of PD were identified via questionnaires and subsequently confirmed by reviewing medical records. We used Cox proportional hazard models to calculate cohort-specific HRs, and used fixed-effects models to calculate the pooled HR.

Results: During 26 y of follow-up, we identified 601 incident PD cases (296 women and 305 men). After adjusting for potential covariates, the pooled HR for the highest compared with the lowest quintile of dietary nicotine intake was 0.70 (95% CI: 0.51, 0.94). The significant inverse association was, however, only observed in women (adjusted HR: 0.64; 95% CI: 0.42, 0.96), not in men (adjusted HR: 0.77; 95% CI: 0.50, 1.20). Further adjusting for environmental tobacco smoke exposure, family history of PD, and use of ibuprofen generated similar significant results in women. Consistently, greater consumption of peppers was associated with lower risk of PD (adjusted HR for ≥5 times/wk compared with ≤3 times/mo: 0.49; 95% CI: 0.25, 0.94) in women but not in men (adjusted HR: 1.04; 95% CI: 0.57, 1.90).

Conclusions: Women with greater dietary nicotine intake had a lower risk of PD than those with lower intake. *Am J Clin Nutr* 2020;112:1080–1087.

Keywords: dietary nicotine, Parkinson disease, prospective study, neurodegenerative disease, cohort

Introduction

Parkinson disease (PD) is a progressive neurodegenerative disorder characterized by tremor, rigidity, and bradykinesia, as the consequence of the degeneration of dopaminergic neurons in the substantia nigra (1). According to the latest Global Burden of Disease Study, PD has become the fastest growing in prevalence, disability, and deaths among all neurological disorders (2). Among all reported risk factors for PD, tobacco use, including cigarette smoking (3–6), smokeless tobacco use (5, 7, 8), and exposure to environmental tobacco smoke (9–11), was consistently observed to be associated with a lower risk of PD in previous epidemiologic studies. For example, in a pooled prospective study with 10–20 y of follow-up, compared with never-smokers, the age-adjusted rate ratios for PD were 0.4 for current smokers and 0.6 for past smokers (3). Of the thousands of compounds from tobacco smoke, nicotine is an obvious candidate because it is responsible for the addictive properties of tobacco and is known to modulate dopaminergic function in the striatum, a brain region of particular relevance to PD (12, 13).

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Supplemental Table 1 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

The data sets analyzed in the current study are not publicly available because of restricted access, but further information about the data sets is available from the corresponding author on reasonable request.

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Abbreviations used: AHEI, Alternate Healthy Eating Index; HPFS, Health Professionals Follow-up Study; nAChR, nicotinic acetylcholine receptor; NHS, Nurses' Health Study; NSAID, nonsteroidal anti-inflammatory drug; PD, Parkinson disease.

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Tobacco use itself causes inherent health problems and decreases life expectancy (14, 15), yet other members of the Solanaceae family (*Nicotiana* sp.) also produce nicotine, including *Capsicum* and *Solanum* whose edible fruits and tubers include peppers, tomatoes, and potatoes (16). Although it might be assumed that exposure to dietary nicotine is negligible compared with the amount obtained from active smoking, and probably lower than that obtained from passive smoking, data suggest that a substantial portion of nicotinic acetylcholine receptors (nAChRs) of most or all subtypes could be occupied even when exposed to relatively small amounts of environmental tobacco smoke, much lower than that from active smoking (17). Consistent with this notion, a retrospective case-control study that included 490 PD cases and 644 controls showed an inverse association of greater consumption of nicotine from edible Solanaceae and peppers, the major contributor for dietary nicotine, with lower odds of having PD (18). The association between dietary nicotine and PD risk has, however, not been examined in prospective studies yet, particularly in never-smokers. There is a high possibility that the amount of nicotine from active smoking would outweigh that from dietary sources. Thus, we reviewed data from >50,000 never-smokers from the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) cohorts from 26 y of follow-up to prospectively investigate potential associations between consumption of dietary nicotine and nicotine-containing foods and future risk of PD.

Methods

Study population

The HPFS cohort was established in 1986, when 51,529 male US health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians) aged 40–75 y responded to a mailed questionnaire, answering questions regarding their medical histories and health-related behaviors. The NHS cohort began in 1976, when 121,700 female registered nurses aged 30–55 y responded to a similar questionnaire. Members of both cohorts have been mailed follow-up questionnaires every 2 y to update information on potential risk factors and to ascertain newly diagnosed diseases. Dietary intake data have been collected since 1980 in the NHS and 1986 in the HPFS. Because peppers are a main source of dietary nicotine (16) and data on them were not collected until 1986, we used the year 1986 as baseline for both the HPFS and the NHS in the current analysis.

We excluded the following individuals: *1*) those who reported as an ever smoker or cigar/pipe user at baseline and during follow-up; *2*) those with implausible total energy intake (<800 kcal/d or >4200 kcal/d for men and <600 kcal/d or >3500 kcal/d for women); *3*) those with a diagnosis of PD at baseline; and/or *4*) those with missing baseline dietary information, leaving 19,523 men and 31,615 women in the current study (**Supplemental Figure 1**).

This study was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard TH Chan School of Public Health.

Assessment of dietary nicotine (exposures)

Usual diet was assessed through semiquantitative FFQs which were validated for use with these populations (19, 20). Participants were asked how often over the past year they consumed a commonly used portion of each food with 9 possible responses ranging from "never" to "six or more times per day." Nutrient intakes were calculated by multiplying the frequency response by the nutrient content of the specified portion size, based on data from the USDA and supplemented with manufacturer information.

The Solanaceae family edibles include peppers (including green, yellow, and red), tomatoes, processed tomatoes (i.e., tomato sauce and tomato juice), and potatoes (baked or mashed) (16). Because nicotine concentrations are high in tea leaves (16), we also included tea as a source of dietary nicotine in the current analysis. In addition to the frequency per day of each nicotine-containing food, we created a combined variable by summing nicotine concentration of the individual Solanaceae foods, based on the most sensitive comprehensive laboratory analysis of nicotine in edible Solanaceae published to date (16). More precisely, the mean nicotine concentration was used as the amount which would be consumed for all Solanaceae foods. We used the mean value of 6.5 μg nicotine/kg for calculating nicotine concentrations in peppers (16). For tomatoes we only included measurements for fresh, ripe tomatoes (degree of ripening: 7–12; mean: 2.7 μg nicotine/kg) (16). For tomato juice and tomato sauce, we used all measurements for processed tomato products (mean: 5.7 μg nicotine/kg). For potatoes we used the mean value of 4.5 μg nicotine/kg (16). For tea, we used the mean value of nicotine concentrations (4 μg nicotine/L) in all brewed tea (16). In the validation study of the FFQs which were used in the current study, the validity correlations were 0.38 for peppers, 0.40 for tomatoes, 0.11 for tomato juice, 0.37 for tomato sauce, 0.45 for potatoes, and 0.69 for tea (19).

Assessment of covariates

Information on other covariates of interest, including age, weight, height, smoking status, and physical activity, was also collected via self-report questionnaires for both cohorts. Information on environmental tobacco use was collected in 1982 for the NHS and 2004 for the HPFS via questionnaires. The questions included whether the study participant was currently exposed to second-hand smoke from other people at home or at work, and the responses were categorized into 4 levels—no exposure, occasional exposure, regular exposure at home or at work, and regular exposure at home and at work. Information on family history of PD (father, mother, and siblings) was collected in 2008. BMI was calculated as kg/m^2. Because carotenoids have been suggested to be neuroprotective (21), we included total carotenoid intake in the analysis, including α-carotene, β-carotene, lutein-zeaxanthin, lycopene, and β-cryptoxanthin. Because ibuprofen was reported to be associated with a lower risk of PD (22), we collected information on use of ibuprofen and other nonsteroidal anti-inflammatory drugs (NSAIDs) in 1986 for men and 1990 for women. For women participants, we also ascertained data on menopausal status and postmenopausal hormone use.

Based on dietary intake data, we calculated the Alternate Healthy Eating Index (AHEI)-2010 score including 11 components to reflect overall diet quality (23). Specifically, this included 6 components for which higher intakes are better (vegetables, fruit, whole grains, nuts/legumes, long-chain fats, and PUFAs);

1 component for which moderate intake is better (alcohol); and 4 components for which lower intake is better (sugar-sweetened beverages and fruit juice, red/processed meat, *trans* fat, and sodium). Each component has a minimum score of 0 and a maximum score of 10, with the total AHEI-2010 score ranging from 0 (worst) to 110 (best).

Ascertainment of PD cases

Ascertainment of PD cases has been described elsewhere (24). Briefly, potential PD cases were first identified using biennial self-report questionnaires. Before 2003, when individuals indicated a diagnosis of PD, we asked the corresponding treating neurologists to either complete a questionnaire to confirm the diagnosis or send a copy of the patients' medical records. A case was confirmed if the physician considered the PD diagnosis definite or probable or if the medical record included either a final diagnosis of PD by a neurologist or the evidence of ≥2 of 3 cardinal signs of PD (resting tremor, rigidity, bradykinesia) in the absence of features suggesting another diagnosis. In participants who self-reported PD, we systematically ruled out PD-related diseases that were not qualified as "probable or definite PD" because of an alternative (or no) diagnosis, including dementia with Lewy bodies (37.5%), unknown/insufficient information (21.1%), multiple system atrophy (14.7%), vascular Parkinsonism (9.1%), essential tremor (3.8%), progressive supranuclear palsy (3.0%), drug-induced Parkinsonism (2.2%), and other relevant conditions (e.g., corticobasal degeneration, and traumatic brain injury Parkinsonism, 8.6%). Since 2003, the aforementioned procedure was used except that medical records were requested for all self-reported cases and were reviewed by a neurologist specializing in movement disorders. If the movement disorders specialist differed from the neurologist on the disease diagnosis, the decision of the movement disorders specialist was adopted. Death certificates of the deceased study participants were also requested to identify PD diagnoses that were not reported in the regular follow-up (<2%). In the current analyses, we only included confirmed PD cases.

Statistical analysis

Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc.). We computed person-time of follow-up for each participant from the date of returning the baseline FFQ until the date of PD diagnosis, death from any cause, the last completed questionnaire, or the end of follow-up (June 2012 for the NHS and January 2012 for the HPFS), whichever came first. Analyses were stratified by age in months at start of follow-up and calendar year of current questionnaire cycle. We categorized baseline (year 1986) total dietary nicotine intake into quintiles. In terms of individual nicotine-containing foods, we categorized them into 4 groups based on the frequency of consumption: *1*) ≤3 times/mo; *2*) 1 time/wk; *3*) 2–4 times/wk; or *4*) ≥5 times/wk. In each analysis, the lowest intake category was used as the reference group. In primary analyses, we calculated HRs by dividing the incidence rate across categories of total dietary nicotine and individual nicotine-containing foods by the corresponding rate in the reference quintile. Cohort-specific HRs were derived from Cox proportional hazard models, adjusted for age (in months), BMI (<21, 21 to <25, 25 to <30, 30 to <35, or ≥35), physical activity (in quintiles), caffeine intake (in quintiles), alcohol intake (none, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥15 g/d for women and none, 0.1–9.9, 10.0–19.9, 20.0–29.9, or ≥30 g/d for men), total carotenoid intake (in quintiles), total energy intake (in quintiles), overall diet quality as assessed by the AHEI-2010 (25) (in quintiles), menopausal status (women only), and postmenopausal hormone use (women only). We used fixed-effects models to calculate the pooled RR, because *P* values for heterogeneity were > 0.05 for all.

The robustness of the results was tested in sensitivity analyses by further adjusting for exposure to environmental tobacco smoke, family history of PD, and use of other NSAIDs (e.g., ibuprofen), or excluding participants ever exposed to environmental tobacco smoke as secondary analyses. A lagged analysis was conducted excluding the first 4 or 6 y of follow-up in each cohort, respectively, to minimize the possibility that participants experiencing PD symptoms at the time of questionnaire completion might have changed their dietary habits. In addition, we used cumulative updated average nicotine intake from all available questionnaires up to the start of each 2-y follow-up period, categorized by cohort-specific quintile of intake, to represent long-term dietary nicotine intake patterns of individuals. To test the potential effect of high consumption of fruits and vegetables on PD risk, we conducted 2 sensitivity analyses: *1*) testing the association between subtotal nicotine intake from other foods except peppers and PD risk; and *2*) testing the association between fruits and vegetables with low concentrations of nicotine and risk of PD. For the purpose of exploration, we also conducted analyses with regard to dietary nicotine and PD among never-smokers (29,254 men and 41,284 women; 563 incident PD cases).

Likelihood ratio tests were conducted to examine statistical interactions between total nicotine intake and sex, age, caffeine intake, and dietary quality in relation to PD risk, by comparing −2 log likelihood χ^2 values between nested models with and without the cross-product terms.

Results

We identified 601 incident cases (296 in women and 305 in men) during 26 y of follow-up. Participants with higher baseline dietary nicotine intake were more likely to be older and more engaged in physical activity, and had higher intakes of caffeine, alcohol, total carotenoids, and total energy (**Table 1**). Greater consumption of dietary nicotine was associated with lower future PD risk—the pooled adjusted HR comparing participants in the highest dietary nicotine quintile at baseline with those in the lowest quintile was 0.70 (95% CI: 0.51, 0.94), after adjustment for age, BMI, physical activity, alcohol, caffeine, total carotenoid intake, total energy intake, overall dietary patterns, menopausal status (women only), and postmenopausal hormone use (women only). The significant inverse association was only observed in women (adjusted HR: 0.64; 95% CI: 0.42, 0.96), not in men (adjusted HR: 0.77; 95% CI: 0.50, 1.20) (**Table 2**).

In the sensitivity analyses, we observed similar results. When further adjusted for environmental tobacco smoke exposure status, family history of PD, and use of other NSAIDs (e.g., ibuprofen), the adjusted HR of the highest quintile was 0.64

TABLE 1 Age-adjusted characteristics of the study population at baseline by category of total nicotine intake[1]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Nurses' Health Study, 1986–2012	$n = 5818$	$n = 6077$	$n = 6352$	$n = 6635$	$n = 6733$
Age,[2] y	53.0 ± 7.3	53.0 ± 7.3	53.2 ± 7.3	53.4 ± 7.3	52.8 ± 7.4
BMI, kg/m^2	25.5 ± 4.8	25.6 ± 5.1	25.4 ± 4.7	25.7 ± 4.9	25.6 ± 4.9
Caucasian	94.9	97.5	97.7	98.1	98.3
Physical activity, MET-h/wk	13.8 ± 20.4	13.9 ± 20.7	14.0 ± 17.7	13.7 ± 17.4	14.1 ± 21.8
Caffeine intake, mg/d	211 ± 211	216 ± 206	230 ± 207	247 ± 195	307 ± 190
Alcohol, g/d	3.4 ± 7.4	3.8 ± 7.8	4.0 ± 8.0	4.1 ± 7.8	3.7 ± 8.1
Total energy intake, kcal/d	1464 ± 439	1697 ± 455	1858 ± 482	1921 ± 534	1976 ± 554
Total carotenoid intake, μg/d	11,411 ± 5385	13,850 ± 5913	16,798 ± 6941	17,850 ± 8502	19,145 ± 10568
Alternate Healthy Eating Index	52.1 ± 11.2	51.2 ± 11.4	51.5 ± 11.0	51.0 ± 10.9	50.3 ± 10.7
Family history of PD	4.7	4.9	5.2	4.5	4.7
Health Professionals Follow-up Study, 1986–2012	$n = 3673$	$n = 4029$	$n = 4014$	$n = 3971$	$n = 3836$
Age,[2] y	52.2 ± 9.7	52.7 ± 9.8	52.9 ± 9.8	54.1 ± 10.0	53.6 ± 9.7
BMI, kg/m^2	25.2 ± 3.2	25.2 ± 3.2	25.2 ± 3.3	25.3 ± 3.3	25.2 ± 3.1
Caucasian	93.2	95.1	96.4	96.1	95.9
Physical activity, MET-h/wk	18.0 ± 23.8	19.1 ± 26.9	20.4 ± 28.0	20.9 ± 28.9	19.6 ± 26.5
Caffeine intake, mg/d	152 ± 197	157 ± 197	157 ± 195	174 ± 187	248 ± 199
Alcohol, g/d	6.7 ± 11.3	7.5 ± 12.3	7.7 ± 11.4	7.5 ± 11.1	7.8 ± 11.8
Total energy intake, kcal/d	1644 ± 502	1883 ± 550	2050 ± 577	2143 ± 628	2267 ± 653
Total carotenoid intake, μg/d	11,218 ± 6528	13,981 ± 6575	17,269 ± 8079	18,948 ± 9510	21,573 ± 13142
Alternate Healthy Eating Index	51.9 ± 11.2	52.7 ± 11.5	53.8 ± 11.6	53.3 ± 11.4	52.6 ± 11.4
Family history of PD	2.9	3.2	3.2	3.0	3.1

[1] Values are means ± SDs or percentages, unless otherwise indicated, and are standardized to the age distribution of the study population. MET, metabolic equivalents from recreational and leisure-time activities; PD, Parkinson disease.

[2] Value is not age-adjusted.

(95% CI: 0.42, 0.97) in women (Table 2). Including total energy intake as a continuous variable generated similar results (data not shown). Restricting to participants without exposure to environmental tobacco smoke or using 4-y or 6-y lag analysis did not materially change the association in women: the adjusted HRs of the highest compared with the lowest quintile were 0.55 (95% CI: 0.24, 1.30), 0.65 (95% CI: 0.43, 1.00), and 0.64 (95% CI: 0.42, 0.98), respectively. When we used the quintiles of cumulative average intake of nicotine as exposures, the adjusted HR was 1.02 (95% CI: 0.34, 3.05) in women. Similar to the results in the primary analysis, a nonsignificant inverse trend persisted in men in the sensitivity analyses (data not shown).

Consistently, greater baseline consumption of peppers was associated with lower risk of PD (adjusted HR for ≥5 times/wk compared with ≤3 times/mo: 0.49; 95% CI: 0.25, 0.94) in women but not in men (adjusted HR: 1.04; 95% CI: 0.57, 1.90). In contrast, we did not find any significant association between other nicotine-containing foods and PD risk (**Table 3**). The association between total nicotine intake and PD risk was not significantly modified by age, sex, caffeine intake, or dietary quality (P-interaction > 0.05 for all).

In addition, greater nicotine intake from other foods except peppers was also marginally significantly associated with lower PD risk (adjusted HR: 0.74; 95% CI: 0.55, 1.00). In contrast, the association between consumption of low-nicotine fruits and vegetables and PD risk was not significant (**Supplemental Table 1**).

In the exploratory analysis, there was no significant association between total nicotine intake and PD risk among ever tobacco users (adjusted HR for the highest compared with the lowest quintile: 0.99; 95% CI: 0.74, 1.34). A similar sex-difference was observed: the adjusted HR comparing the 2 extreme quintiles was 0.79 (95% CI: 0.51, 1.22) in women and 1.23 (95% CI: 0.81, 1.86) in men.

Discussion

In this large prospective study, higher dietary nicotine intake was associated with lower risk of PD, particularly in women, independently of potential co-determinants, comprising age, sex, BMI, physical activity, alcohol intake, caffeine intake, total carotenoid intake, total energy intake, overall dietary patterns, menopausal status, and postmenopausal hormone use. A significant relation also was observed between greater consumption of peppers and lower PD risk in women.

Previous studies have shown consistently that tobacco use, either active (3–8) or passive (9–11), was associated with a lower risk of PD. This inverse association is reported to be influenced by both dose (3) and duration (26) of smoking. Individuals with more years smoked, more cigarettes per day, older age at quitting smoking, and fewer years since quitting smoking had lower PD risk (27).

In this study, we observed an inverse association between dietary nicotine intake and risk of developing PD in the future. The results were consistent with a retrospective case-control study of edible Solanaceae consumption and PD risk in which 490 newly diagnosed idiopathic PD cases were included (18). An inverse association was found between the frequency of consumption of edible Solanaceae and PD risk, and when those foods were weighted by nicotine concentration, the inverse PD–Solanaceae association became strengthened (P-trend = 0.004) (18). This case-control study also showed a significant inverse association for peppers: eating peppers ≥2 times/wk was associated with ≥30% lower odds for PD (18). Similarly, in the

TABLE 2 Adjusted HRs and 95% CIs of PD by category of total nicotine intake at baseline[1]

Nicotine consumption	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{trend}
Women						
Median, μg	0.31	0.59	0.87	1.30	2.78	
Cases, *n*	59	55	56	71	55	
Person-years	134,902	142,362	148,948	154,916	157,694	
Crude incidence rate, per 100,000 person-years	44	39	38	46	35	
HR (95% CI)						
Age adjusted	1 (Ref.)	0.86 (0.60, 1.25)	0.83 (0.57, 1.20)	1.00 (0.70, 1.41)	0.78 (0.54, 1.14)	0.35
Age and total energy adjusted	1 (Ref.)	0.79 (0.54, 1.15)	0.73 (0.50, 1.07)	0.87 (0.60, 1.25)	0.68 (0.46, 1.00)	0.15
Multivariate[2]	1 (Ref.)	0.79 (0.54, 1.15)	0.72 (0.48, 1.06)	0.87 (0.59, 1.26)	0.64 (0.42, 0.96)	0.09
Further adjusted for environmental tobacco smoke exposure status,[3] family history of PD,[4] and other NSAID use (e.g., ibuprofen)[5]	1 (Ref.)	0.79 (0.54, 1.15)	0.72 (0.48, 1.06)	0.86 (0.59, 1.26)	0.64 (0.42, 0.97)	0.10
Men						
Median, μg	0.27	0.52	0.76	1.12	2.00	
Cases, *n*	57	63	62	70	53	
Person-years	78,818	87,043	87,084	84,313	82,740	
Crude incidence rate, per 100,000 person-years	72	72	71	83	64	
HR (95% CI)						
Age adjusted	1 (Ref.)	0.99 (0.68, 1.42)	0.92 (0.63, 1.33)	1.00 (0.70, 1.43)	0.76 (0.52, 1.12)	0.16
Age and total energy adjusted	1 (Ref.)	0.97 (0.66, 1.40)	0.88 (0.60, 1.29)	0.95 (0.65, 1.38)	0.71 (0.48, 1.07)	0.09
Multivariate[2]	1 (Ref.)	0.97 (0.66, 1.42)	0.87 (0.59, 1.29)	0.96 (0.65, 1.44)	0.77 (0.50, 1.20)	0.26
Further adjusted for environmental tobacco smoke exposure status,[3] family history of PD,[4] and other NSAID use (e.g., ibuprofen)[5]	1 (Ref.)	0.96 (0.65, 1.40)	0.88 (0.59, 1.31)	0.98 (0.65, 1.46)	0.81 (0.52, 1.26)	0.37
Pooled analysis[6]						
Multivariate[2]	1 (Ref.)	0.87 (0.67, 1.14)	0.79 (0.60, 1.04)	0.91 (0.69, 1.20)	0.70 (0.51, 0.94)	0.04
Further adjusted for environmental tobacco smoke exposure status,[3] family history of PD,[4] and other NSAID use (e.g., ibuprofen)[5]		0.87 (0.66, 1.14)	0.79 (0.60, 1.04)	0.91 (0.69, 1.20)	0.71 (0.52, 0.96)	0.06

[1]NSAID, nonsteroidal anti-inflammatory drug; PD, Parkinson disease.

[2]Adjusted for age, BMI, physical activity, caffeine, alcohol, total carotenoid intake, total energy intake, overall dietary patterns, postmenopausal status, and current postmenopausal hormone use (premenopausal/postmenopausal without hormone use/postmenopausal with hormone use, women only).

[3]Environmental tobacco smoke exposure status was collected in 1982 for women and 2004 for men.

[4]Family history of PD (father, mother, and siblings) was collected in 2008.

[5]Other NSAID use (e.g., ibuprofen) was collected in 1990 for women and 1986 for men.

[6]Fixed-effects model was used, *P*-heterogeneity = 0.98.

current study, we observed a 52% lower PD risk for women when eating ≥5 times/wk, relative to those eating ≤3 times/mo. We did not see a significant inverse association between either total nicotine intake or individual nicotine-containing foods and PD risk in men. There is a possibility that women had higher nicotine intake with larger variations across each quintile than men, such that the effect size was greater. Despite a smaller sample size in men, the number of male PD cases was larger, suggesting the statistical power might not be reduced. It is also possible that the sex-difference was due to chance.

One mechanism that has been proposed to explain the apparent association between nicotine and lower risk of PD is through a close anatomical relation between the cholinergic and dopaminergic neurotransmitter systems in the striatum (28). The striatum receives abundant cholinergic innervation, and the neurons of the striatum express several types of both metabotropic muscarinic cholinergic receptors and ionotropic nAChRs. The most obvious hypothesis is that premorbid exposure to nicotine somehow influences the cholinergic modulation of dopamine systems in a way that decreases disease progression (29–33). Another novel hypothesis posits that nicotine exerts its effect by changing the composition of the microbiota in the gut in a way that mitigates intestinal inflammation (34–36). The reduced inflammation would lead to less misfolding of α-synuclein, decreasing the misfolded forms that might propagate the disease to the central nervous system causing neurodegeneration (34). Clearly additional research is required to ascertain precise mechanisms.

Compared with the nicotine concentration in cigarettes (*c*.900–1700 μg nicotine is assumed to be absorbed from a single cigarette), the daily dietary nicotine intake is 3 orders of magnitude lower. As expected, we did not see a significant inverse association among ever tobacco users in the current study, which is consistent with the previous case-control study,

TABLE 3 Adjusted HRs and 95% CIs of Parkinson disease by intake of individual nicotine-containing foods at baseline[1]

Nicotine-containing food	Categories (frequency)				P_{trend}
	≤3 times/mo	1 time/wk	2–4 times/wk	≥5 times/wk	
Peppers					
Women					
Median total nicotine intake, μg/d	0.80	0.95	1.09	1.31	
Median nicotine intake from peppers, μg/d	0.02	0.03	0.10	0.19	
Cases, *n*	182	63	41	10	
Person-years	426,488	165,467	103,592	43,276	
HR (95% CI)	1 (Ref.)	0.89 (0.66, 1.19)	0.84 (0.59, 1.21)	0.49 (0.25, 0.94)	0.03
Men					
Median total nicotine intake, μg/d	0.68	0.82	0.97	1.24	
Median nicotine intake from peppers, μg/d	0	0.03	0.10	0.19	
Cases, *n*	198	54	36	14	
Person-years	270,623	79,130	46,739	16,140	
HR (95% CI)	1 (Ref.)	0.93 (0.68, 1.28)	1.04 (0.71, 1.53)	1.04 (0.57, 1.90)	0.85
Pooled analysis[2]	1 (Ref.)	0.91 (0.73, 1.13)	0.93 (0.71, 1.21)	0.73 (0.47, 1.15)	0.16
Tomatoes					
Women					
Median total nicotine intake, μg/d	0.60	0.72	0.96	1.24	
Median nicotine intake from tomatoes, μg/d	0.02	0.05	0.14	0.26	
Cases, *n*	48	77	118	53	
Person-years	138,807	185,242	264,133	150,641	
HR (95% CI)	1 (Ref.)	1.17 (0.81, 1.70)	1.11 (0.78, 1.59)	0.86 (0.55, 1.32)	0.28
Men					
Median total nicotine intake, μg/d	0.50	0.62	0.80	1.13	
Median nicotine intake from tomatoes, μg/d	0.02	0.05	0.14	0.26	
Cases, *n*	46	81	120	57	
Person-years	78,716	106,638	152,238	79,099	
HR (95% CI)	1 (Ref.)	1.44 (0.98, 2.11)	1.28 (0.87, 1.86)	0.98 (0.63, 1.54)	0.38
Pooled analysis[2]	1 (Ref.)	1.30 (0.99, 1.69)	1.19 (0.91, 1.54)	0.91 (0.67, 1.25)	0.17
Processed tomatoes					
Women					
Median total nicotine intake, μg/d	0.65	0.82	1.02	1.44	
Median nicotine intake from processed tomatoes, μg/d	0.05	0.10	0.22	0.43	
Cases, *n*	90	99	81	26	
Person-years	223,658	249,715	187,729	77,721	
HR (95% CI)	1 (Ref.)	1.05 (0.78, 1.43)	1.15 (0.80, 1.64)	0.80 (0.47, 1.37)	0.70
Men					
Median total nicotine intake, μg/d	0.60	0.68	0.87	1.32	
Median nicotine intake from processed tomatoes, μg/d	0.05	0.10	0.22	0.43	
Cases, *n*	126	77	57	45	
Person-years	149,652	126,329	97,977	46,041	
HR (95% CI)	1 (Ref.)	0.72 (0.53, 0.98)	0.68 (0.47, 0.98)	0.90 (0.57, 1.43)	0.54
Pooled analysis[2]	1 (Ref.)	0.87 (0.70, 1.08)	0.89 (0.69, 1.15)	0.86 (0.61, 1.22)	0.48
Potatoes					
Women					
Median total nicotine intake, μg/d	0.49	0.65	0.98	1.47	
Median nicotine intake from potatoes, μg/d	0.07	0.13	0.41	0.75	
Cases, *n*	57	74	125	40	
Person-years	129,198	206,124	315,369	88,132	
HR (95% CI)	1 (Ref.)	0.83 (0.59, 1.19)	0.78 (0.56, 1.09)	0.79 (0.51, 1.22)	0.29
Men					
Median total nicotine intake, μg/d	0.41	0.54	0.88	1.34	
Median nicotine intake from potatoes, μg/d	0.07	0.13	0.41	0.75	
Cases, *n*	44	87	138	34	
Person-years	77,235	128,684	171,305	39,735	
HR (95% CI)	1 (Ref.)	1.20 (0.82, 1.75)	1.27 (0.88, 1.82)	1.01 (0.62, 1.65)	0.89
Pooled analysis[2]	1 (Ref.)	0.99 (0.77, 1.28)	0.97 (0.76, 1.24)	0.88 (0.64, 1.22)	0.51
Tea					
Women					
Median total nicotine intake, μg/d	0.59	0.75	1.02	1.98	
Median nicotine intake from tea, μg/d	0	0.13	0.41	0.95	
Cases, *n*	152	20	39	85	
Person-years	367,252	65,350	81,474	224,746	
HR (95% CI)	1 (Ref.)	0.73 (0.45, 1.17)	1.16 (0.81, 1.66)	0.88 (0.66, 1.18)	0.61

(*Continued*)

TABLE 3 (*Continued*)

Nicotine-containing food	Categories (frequency) ≤3 times/mo	1 time/wk	2–4 times/wk	≥5 times/wk	P_{trend}
Men					
Median total nicotine intake, μg/d	0.56	0.70	0.99	1.74	
Median nicotine intake from tea, μg/d	0	0.13	0.41	0.95	
Cases, *n*	179	30	33	54	
Person-years	231,042	41,409	46,740	91,472	
HR (95% CI)	1 (Ref.)	1.02 (0.68, 1.53)	0.99 (0.65, 1.51)	0.91 (0.64, 1.30)	0.62
Pooled analysis[2]	1 (Ref.)	0.89 (0.65, 1.21)	1.08 (0.82, 1.42)	0.89 (0.72, 1.12)	0.48

[1]Adjusted for age, BMI, physical activity, caffeine, alcohol, total carotenoid intake, total energy intake, overall dietary patterns, postmenopausal status, and current postmenopausal hormone use (premenopausal/postmenopausal without hormone use/postmenopausal with hormone use, women only).
[2]Fixed-effects model was used, *P*-heterogeneity > 0.05. *P*-interaction for sex > 0.05.

in which the authors did not observe a significant association between frequency of consumption of edible Solanaceae and PD risk among ever tobacco users (RR: 0.89; 95% CI: 0.68, 1.17) (18). In terms of passive smoking, according to a large US population-based study, the median value of serum cotinine was 0.5 ng/mL in populations reporting home or work environmental tobacco smoke exposure (37), which corresponds to a daily intake of 40 μg nicotine (38). Among individuals only exposed to tobacco smoke through passive smoking at home, the number of years living with a daily smoker was significantly associated with lower PD risk (OR: 0.86/y; 95% CI: 0.75, 0.99/y) (9). Positron emission tomography imaging studies have shown that a substantial proportion of nAChRs are occupied at low blood nicotine concentrations; indeed, 1–2 puffs of a cigarette result in 50% occupancy of nAChRs for >3 h after smoking (17). It is also possible, however, that components other than nicotine in these foods might exert the underlying effects on PD risk.

In a sensitivity analysis of the current study, we excluded participants with environmental tobacco smoke exposure to minimize the possibility that nicotine from tobacco would likely eclipse that from dietary sources, and observed an even stronger result, albeit at a nonsignificant level probably owing to a small sample size. We only had 1-time information on environmental tobacco smoke; as such, there may be residual confounding of the nicotine–PD relation because people were likely still exposed to some environmental smoke because smoking was permitted in public in most states until the mid-2000s. Nonetheless, previous studies of passive smoking using the same populations and information on exposure to environmental tobacco use have supported its reliability (39, 40).

Alternately, the observed nicotine–PD relation could be confounded by other unknown components in peppers because the significant association was not observed for other individual nicotine-containing foods, and the median nicotine intake from peppers was lower than from other nicotine-containing foods. However, greater consumption of subtotal nicotine from the other foods except peppers was also marginally significantly associated with lower PD risk, although the association became weaker than for nicotine from peppers. This suggests a possibility of synergistic effects of nicotine and other components in peppers. Further studies are warranted to examine this speculation.

Our study has strengths and limitations that deserve mention. Two major strengths are the fact that this is the first prospective study investigating dietary nicotine intake and PD risk to date, to our knowledge, and it has a large sample size. In addition, the prospective nature reduces the potential for reverse causation and recall bias. Further, both cohorts had high follow-up rates and detailed validated dietary information. Another strength is the ability to control for various potential confounders and known risk factors for PD. On the other hand, because of the observational study design, the possibility for residual confounding cannot be eliminated fully. We also could not completely exclude the possibility that the results observed in the current study were by chance because a significant association was only observed in women but not in men, although the significance persisted in sensitivity analyses. Moreover, we admit that there might be potential measurement errors from the FFQs. However, they have been validated in both cohorts (19, 20, 41), and our results would be expected to be biased toward the null owing to any measurement error because it is likely to be nondifferential to PD because of our prospective design.

In conclusion, consumption of dietary nicotine and nicotine-rich foods like peppers was associated with lower risk of PD, particularly in women. This result should be interpreted with caution because of the observational study design and inconsistent results in men and women. Further research is needed to replicate our findings in different populations and to elucidate the mechanisms involved in this association.

The authors' responsibilities were as follows—XG: designed the research; AA: provided essential materials; CM: analyzed the data, performed the statistical analysis, and wrote the paper; and all authors: had primary responsibility for the final content and read and approved the final manuscript. The authors report no conflicts of interest.

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