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Passive smoking and Parkinson's disease in California Teachers

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ABSTRACT

Introduction: Tobacco smoking is consistently inversely associated with Parkinson's disease (PD) in men and women; recently this has been related to reverse causation, prompting questions as to whether similar patterns exist for passive smoke exposure. We used baseline and follow-up data from the California Teachers Study, a prospective cohort of women, to investigate whether timing, location and cumulative measures of intensity and duration of passive smoke exposure are associated with PD risk.
Methods: Using a nested case-control approach, we included 224 diagnostically validated cases (158 with no history of personal smoking) and selected 3230 age- and race-matched controls (1973 with no history of personal smoking). We estimated odds ratios(ORs) and 95% confidence intervals(CI) by fitting adjusted multivariable unconditional logistic regression models.
Results: Among lifelong non-smokers, passive smoke exposure combined across all settings and accumulated over a lifetime was not associated with PD risk (OR = 1.18, 95% CI 0.60, 2.30). Workplace exposure was also not associated with risk. Household exposure during adulthood but not childhood was inversely associated with PD (OR = 0.59, 95% CI 0.40, 0.87). Exposure to passive smoke in other social settings was positively associated with PD (OR = 1.62, 95% CI 1.11, 2.36). These contradictory results may be attributable to chance due to multiple comparisons in subgroup analyses. No pattern emerged to suggest that increasing years of passive smoke exposure, smokiness of the setting, or combined smokiness by exposure years was associated with lower PD risk.
Conclusion: Results do not convincingly support a protective effect of passive smoking in PD.

1. Introduction

Epidemiologic studies have consistently found moderate to strong inverse dose-response relationships between personal tobacco smoking and Parkinson's disease(PD) in men and women [1–5]. More than one hypothesis has been proposed to explain these observations [6,7]. Some studies point to a biological basis [6,8] supported by experimental studies showing that cigarette smoke prevents the breakdown of dopamine by inhibiting monoamine oxidase, stimulates the release of dopamine, and may protect against hydrogen peroxide-induced membrane damage [9–11]. Alternative non-causal explanations include limitations inherent in epidemiologic study designs. Even in sophisticated cohort studies, residual confounding due to unmeasured factors, selection or survivor biases, or reverse causation - an important but difficult bias to address - may account for observed associations. For example, we recently proposed that preclinical PD impacts smoking behavior such that patients lose their response to nicotine prior to diagnosis, and are able to stop smoking earlier and more easily than other smokers [12].

Cigarette smoke is comprised of more than 5000 chemicals [13], and the composition of tobacco sidestream smoke is qualitatively similar with respect to chemical number and type, but quantitatively different in the amount or level of exposure to those chemicals [14]. Few studies have examined whether exposure to sidestream smoke (also called passive smoking) is associated with a reduced PD risk [6,15–18]. While two studies suggested exposure-response relationships [6,16], one controlled for personal(active)

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smoking, and in this study, the confidence limits for the risk estimates did not exlude the null hypothesis [16]. Most existing studies have been small, did not always include a truly unexposed reference group, or, importantly, did not estimate passive smoking effects independent of personal smoking. Research on passive smoking provides additional information as to whether cigarette smoke(or one of its constituents) may reduce risk of PD. If no association with passive smoking is found, this could suggest that either the dose from passive smoke exposure is too low to confer protection, or that no underlying biological mechanism exists. On the other hand, if findings are consistent with personal smoking, this could strengthen the arguments for a causal relation or lead to alternate hypotheses explaining how tobacco smoke is associated with PD.

The California Teachers Study(CTS) is a prospective cohort study of women [19] that collected comprehensive data to characterize passive smoke exposure across age periods and settings(home, workplace, and social) with temporal, situational and lifetime measures of exposure to passive smoking [20]. Here we use these data to investigate the association between passive smoke exposure and PD in women taking into consideration history of personal smoking.

2. Methods

2.1. Study population

The CTS was established in 1995–1996 to study breast cancer and other women's health issues [19]. Active, recently active, and retired female members of the California State Teachers Retirement System(STRS) received an invitation to join the cohort by mail, and 133,479 women enrolled by completing the baseline questionnaire. The cohort is being followed annually for hospitalizations, cancer incidence and mortality. Over 20 years of follow-up, women have been mailed four additional questionnaires, collecting data on exposures or other health outcomes of interest.

In 2005, a third follow-up questionnaire was completed by 72,265 active cohort members; it included an item, “Were you ever told by a health professional that you have Parkinson's disease? At what age?” Of 69,527 who provided a response to this item, 404 answered “yes”, and were identified as potential PD cases; 230 (70.3%) of these were later diagnostically validated as possible or probable PD [21]. Controls($n = 3266$) were selected randomly from respondents to the third follow-up questionnaire who had not answered “yes” to the PD question, using frequency matching(1:10 ratio) based on birth year(5-year categories) and race of cases. The present study includes in separate analyses (i) 224(97.3%) cases and 3230 of 3266(98.9%) controls who provided information on active and passive smoking exposure on the baseline questionnaire who may have personally smoked, and (ii) 158(70.5%) cases and 1973(61.1%) controls who reported no personal history of ever actively smoking. The study protocol was approved by institutional review boards at each of the participating institutions.

2.2. Assessment of active and passive smoking exposure

At baseline, women were asked whether they had smoked at least 100 cigarettes. Women who answered “yes” were considered ever smokers (either formerly or currently). Women were identified as lifelong personal active non-smokers if they responded negatively. Two questions broadly assessed childhood or adulthood exposure to passive smoke at home, and women who reported exposure during either time period were considered to have ever been exposed to household passive smoke during childhood or adulthood, respectively. We created a variable that combined personal and passive smoking(no personal smoking and no passive smoke exposure; no personal smoking but exposed to passive smoke; cigarette smoker with or without passive smoke exposure). The latter group collapsed across passive smoking categories as the proportion of women who were personal smokers but unexposed to passive smoke was small(about 5%; 13 PD cases).

In 1997, a follow-up questionnaire which included a more detailed assessment of passive smoke exposure was sent to surviving cohort members; 99,213 women reported their lifetime passive smoke exposure in three settings(household exposure to a smoking spouse, parent, roommate; smokers in the workplace; and exposure to smoke in non-work/social settings) during six age periods(<20, 20's, 30's, 40's, 50's, and 60's + years). Passive smoke exposure was further assessed for duration and intensity at each setting in each age period as follows: duration was estimated by number of years exposed(<6, 6-10, 11-15 and 16 + years for the age period <20 years; < 1 year, 1-3 years, 4-6 years, and 7 + years for 10-year age periods beginning with the 20's). Smoke intensity was estimated by a qualitative description of smoke intensity(“a little smoky”, “fairly smoky”, or “very smoky”).

Following our previous work [22], duration and intensity categorical responses within each combination of setting and age period were transformed to numeric values. For years during the age period, the midpoints of the response ranges were used. For the qualitative smoke intensity, values of 1(“a little smoky), 2(“fairly smoky”) or 3(“very smoky”) were assigned.

The average age at diagnosis reported by women with PD in our study was 68.3 years. As evidence from imaging, pathology, clinical, epidemiologic, and animal studies supports a preclinical phase as preceding PD diagnosis by as little as 2 years and possibly more than 20 years [23–26], and we were interested in historical passive smoke exposures prior to diagnosis, we considered the following age periods in order to capture exposure during childhood(ages 0-19 years), the 20's and 30's, the 40's and 50's, and adulthood(age periods 20's-50's). We did not consider exposure during the 60's, to allow for a latency period prior to diagnosis. Duration of exposure during childhood was based on the 0-19 year age period, and for adulthood we summed the years of exposure reported for each age period(i.e., using the midpoint of the range of years). Similarly, for intensity of exposure, childhood was considered the 0-19 year age period, and for adulthood, we averaged the numerical intensity score of each age period.

Also similar to our previous work [22], we created a summary metric(intensity-years) that incorporated both exposure duration(years) and intensity(smokiness of the setting). A measure of “intensity-years” was created for each combination of setting and age period by multiplying the number of years exposed by level of smoke intensity. These within-setting intensity-years measures for a respondent were tabulated for childhood(0-19 years), the 20's-30's and 40's-50's age periods, and summed for these four individual age periods to calculate that for adulthood.

Finally, we calculated “lifetime” exposure at each setting for duration, intensity and intensity-years by summing the setting-specific values for childhood and adulthood. Lifetime exposures were categorized as above or below the mean using the distribution of each cumulative exposure measure among controls with non-zero values of passive smoke exposure.

2.3. Statistical analysis

Race was categorized as white or other race; women who did not report their race were grouped in the latter category. Multivariable unconditional logistic regression models adjusted for age(continuous), race(white, other) and an indicator of neighborhood socioeconomic status(SES) (low: 1st and 2nd quartile, middle:

3rd quartile, high: 4th quartile) were fit to data to estimate PD risk as odds ratios(ORs) with 95% confidence intervals(CI) for the OR.

First, we examined the individual and joint effects of personal active and passive smoking reported on the baseline questionnaire using the categorical variable that combined exposure to passive smoke and personal smoking history using women who had never smoked and had no passive smoke exposure as the reference category. These results are presented in Table 2.

Second, we examined passive smoke exposure among lifelong non-smokers in more detailed analyses that restricted our sample to 158 cases and 1973 controls who were never smokers at baseline, and who also provided data on passive smoke exposure in the first follow-up questionnaire(4 cases and 29 controls did not provide baseline data on passive smoking during childhood or adulthood). For age-specific or setting-specific exposures, models included binary variables(exposed, unexposed) for each age period of potential exposure(childhood, 20's-30's, 40's-50's, adulthood) or setting(-home, workplace, other social setting); women with no passive smoke exposure served as the reference group. For analyses of duration, intensity and intensity-years, models included a three-level categorical variable for exposure: “none”, “below the mean”, “at or above the mean”, and women unexposed to passive smoke served as the reference group. Linear tests for trend across exposure categories were considered statistically significant at p-trend <0.05. These results are presented in Tables 3 and 4.

All analyses used SAS version 9.4(SAS Institute Inc., Cary, NC, USA.).

3. Results

Cases of PD and controls were predominantly white, of similar age, with a majority being lifetime non-smokers(61%) (Table 1). More controls than cases reported ever smoking, and they had also smoked more pack-years. Using baseline data from all cases and controls, the adjusted OR of PD from exposure to household passive smoking during childhood or adulthood and with no history of personal smoking was 0.85(95% CI, 0.60, 1.20) compared with women who had never personally smoked and who had no exposure to passive smoke(Table 2).

Using more detailed passive smoking data from the second questionnaire among cases and controls with no history of personal smoking, we found no association between any lifetime exposure to passive smoke across all settings(home, work, other social) and PD risk(OR = 1.18, 95% CI 0.60, 2.30). Further, PD risk was not associated with exposure at any setting during age-specific periods including childhood, ages 20's-30's or 40's-50's, or adulthood (Table 3). Exposure in the home overall was not associated with risk of PD, but after adjusting for exposure in other settings and age periods, household exposure specifically during adulthood was inversely associated(OR = 0.59, 95% CI 0.40, 0.87). After adjusting for exposures in non-social settings and during other age periods, any exposure to passive smoke in other social settings(OR = 1.62, 95% CI 1.11, 2.36), and specifically during the 20's-30's age period, was associated with an increased risk of PD. Exposure to passive smoke at the workplace overall or for specific age periods was not associated with PD risk.

Finally, results from analyses among never smokers examining cumulative duration, intensity and intensity-years of passive smoke exposure across all settings did not support an inverse association between the passive smoke exposure measure and PD risk(Table 4).

4. Discussion

In this case-control study of Parkinson's disease nested within the California Teachers Study, risk of PD was not associated with any cumulative measure of passive smoke exposure duration or intensity from three different settings or across various age periods. The contradictory results of a reduced PD risk associated with exposure to passive smoke in the home during adulthood and exposure at other social, non-household and non-workplace settings did not follow any consistent pattern, are difficult to explain, and may be due to chance.

Three case-control and two cohort studies previously examined passive smoke exposure and PD risk [6,15–18]. The case-control studies had both home and workplace passive smoke exposures; among never smokers, results were mixed. No association with risk

Table 1
Characteristics at baseline of Parkinson's disease cases and unaffected controls, California Teachers Study, by history of personal smoking.

Characteristic: Mean ± SD or n (%)	All Cases (n = 224)	All Controls (n = 3230)	Crude OR (95%CI)	Cases with no history of personal smoking n = 158	Controls with no history of personal smoking n = 1973	Crude OR (95%CI)
Age (years) at baseline	64.1 ± 9.2	63.7 ± 9.3	1.00 (0.99, 1.02)	64.5 ± 9.1	63.7 ± 9.8	1.01 (0.99, 1.03)
Age of Parkinson's Disease Diagnosis	68.3 ± 10.5	–	–	68.2 ± 10.6		
Race						
White	208 (92.9)	3017 (93.4)	1.00 (Referent)	145 (91.8)	1820 (92.3)	1.00 (Referent)
Other	16 (7.1)	213 (6.6)	1.10 (0.63, 1.94)	13 (8.2)	153 (7.7)	1.07 (0.59, 1.93)
Neighborhood SES*						
low (1st/2nd quartile)	49 (24.3)	541 (19.0)	1.00 (Referent)	35 (24.8)	356 (20.4)	1.00 (Referent)
middle (3rd quartile)	64 (31.7)	888 (31.1)	0.80 (0.54, 1.17)	48 (34.0)	593 (34.0)	0.82 (0.52, 1.30)
high (4th quartile)	89 (44.1)	1426 (49.9)	0.69 (0.48, 0.99)	58 (41.1)	793 (45.5)	0.74 (0.48, 1.15)
Smoking status (personal)						
never	154 (68.7)	1960 (60.7)	1.00 (Referent)	–	–	–
ever	70 (31.3)	1270 (39.3)	0.70 (0.52, 0.94)	–	–	–
Smoking pack-years	14.9 ± 16.6	17.2 ± 18.1	0.99 (0.98, 1.01)	–	–	–

*22 cases and 375 controls were missing information on SES.

Table 2
Combined effects of personal smoking with childhood or adulthood household passive smoke exposure as reported at baseline among Parkinson's disease cases and controls, California Teachers Study.

Smoking variable	All Cases (n = 224)	All Controls (n = 3230)	Adjusted OR (95% CI)[a]
No personal smoking, No passive smoke exposure	52 (23.2)	585 (18.2)	1.0 (ref)
Passive smoke exposure, No personal smoking	102 (45.5)	1359 (42.3)	0.85 (0.60, 1.20)
Personal smoking with or without passive smoke exposure	70 (30.4)	1267 (38.8)	0.63 (0.44, 0.92)

[a] Adjusted for age, race (white, other), neighborhood SES (tertiles).

Table 3
Associations between passive smoke exposure and Parkinson's disease risk by age and setting among cases and controls with no personal history of smoking, California Teachers Study.

Passive Smoke Exposure[d]	Cases with no history of personal smoking n = 158	Controls with no history of personal smoking n = 1973	Adjusted OR (95% CI)[b]
Any lifetime exposure[a]	128 (81.0)	1617 (82.0)	1.18 (0.60, 2.30)
During childhood (age <20)	87 (55.1)	1114 (56.5)	0.97 (0.66, 1.43)
During 20's-30's	101 (63.9)	1327 (67.3)	0.89 (0.55, 1.45)
During 40's-50's	84 (53.2)	1058 (53.6)	1.01 (0.65, 1.56)
During adulthood (ages 20-59)	114 (72.1)	1456 (73.8)	0.98 (0.58, 1.66)
Any home exposure[c]	100 (63.3)	1366 (69.2)	0.70 (0.46, 1.07)
During childhood (age <20)	73 (46.2)	1013 (51.3)	0.86 (0.59, 1.25)
During 20's-30's	61 (38.6)	933 (47.3)	0.66 (0.43, 1.01)
During 40's-50's	38 (24.1)	525 (26.6)	0.91 (0.57, 1.44)
During adulthood (ages 20-59)	67 (42.4)	996 (50.5)	**0.59 (0.40, 0.87)**
Any workplace exposure[c]	82 (51.9)	1004 (50.9)	1.03 (0.71, 1.51)
During childhood (age <20)	27 (17.1)	284 (14.4)	1.10 (0.68, 1.77)
During 20's-30's	62 (39.2)	786 (39.8)	1.02 (0.65, 1.61)
During 40's-50's	54 (34.2)	700 (35.5)	0.88 (0.56, 1.37)
During adulthood (ages 20-59)	79 (50.0)	967 (49.0)	1.06 (0.71, 1.58)
Any other setting exposure[c]	70 (44.3)	683 (34.6)	**1.62 (1.11, 2.36)**
During childhood (age <20)	34 (21.5)	320 (16.2)	1.25 (0.77, 2.07)
During 20's-30's	63 (39.9)	589 (29.8)	**1.78 (1.05, 3.02)**
During 40's-50's	41 (25.9)	441 (22.4)	0.82 (0.49, 1.38)
During adulthood (ages 20-59)	68 (43.0)	654 (33.2)	1.46 (0.93, 2.28)

[a] Lifetime defined as between birth and age 59.
[b] Adjusted for age and race (white, other), neighborhood SES in tertiles.
[c] OR compare those exposed to passive smoke in the age strata or setting to those unexposed to passive smoke in the age strata or setting, models are mutually adjusted for each other age strata or setting.
[d] Exposure categories are not mutually exclusive therefore individual setting totals will not sum to any exposure.

Table 4
Associations between lifetime passive smoke exposure[a] and PD risk by total years of exposure, intensity of exposure and intensity-years across all settings among cases and controls with no personal history of smoking, California Teachers Study.

Passive Smoke Exposure	Cases with no history of personal smoking n = 158	Controls with no history of personal smoking n = 1973	Adjusted OR (95% CI)[b]	p-trend
Duration, years	33.6 ± 26.2	34.1 ± 25.7		
none	14 (10.0)	187 (10.4)	1.0 (ref)	0.8
<34.0	74 (52.9)	973 (54.1)	1.03 (0.57, 1.87)	
≥34.0	52 (37.1)	638 (35.5)	1.07 (0.58, 1.97)	
Intensity	6.5 ± 5.7	6.7 ± 5.6		
none	17 (12.1)	243 (13.5)	1.0 (ref)	0.87
<6.7	79 (56.4)	951 (52.9)	1.22 (0.71, 2.11)	
≥6.7	44 (31.4)	602 (33.5)	1.05 (0.59, 1.87)	
Intensity-years	42.7 ± 47.1	44.7 ± 42.4		
none	18 (12.9)	247 (13.7)	1.0 (ref)	0.8
<44.6	81 (57.9)	983 (54.7)	1.16 (0.68, 1.98)	
≥44.6	41 (29.3)	566 (31.5)	1.0 (0.56, 1.78)	

[a] Lifetime defined as between birth and age 59.
[b] Adjusted for age and race (white, other), neighborhood SES in tertiles.

of PD was observed in a Japanese hospital-based case-control study that included 185 cases and 222 controls for ever having been exposed to passive smoke at home(OR = 1.17; 95% CI 0.75–1.84) or at work(OR = 1.16; 95% CI 0.77–1.75), although both risk estimates were greater than one. These results contrast with those from a small Australian study of 72 cases and 54 age- and sex-matched neighborhood controls in which the estimated ORs were as low as 0.51 among participants with more than 10 years of workplace and 26 or more years of home exposure to passive tobacco smoke; as was observed in the Japanese study, confidence intervals were wide and included the null value [16]. In a study conducted in Washington that compared 76 cases from a university neurology clinic with 71 controls from a group health plan, strong and statistically significant inverse associations with passive smoking at work(OR = 0.22) or at home(OR = 0.28) were observed [17]. Interestingly, exposure to passive smoke at both locations was not

associated with a risk reduction of similar or greater magnitude, arguing against additive or greater than additive effects. We did not find associations between PD and passive smoke exposure in the workplace, at home or in other settings. We did find a negative association for exposure at home during adulthood but not during childhood, and the latter was offset in our cohort by higher estimated risks due to exposures in other social settings. No association was reported by investigators for one of the two previously published cohort studies. In a study of never smoking Chinese women whose husbands had ever smoked, 42 women were diagnosed with PD during follow-up resulting in an OR for passive smoke exposure of 0.8 that was not statistically significant [15]. The age-adjusted relative risk(RR) in a larger study of 455 PD cases pooled from two cohorts, the Health Profesionals Follow-up Study and the Nurses' Health Study, was 0.85(95% CI 0.67, 1.07) for exposure during childhood to at least one parent smoking. If both parents smoked, the negative association was strengthened (age-adjusted RR = 0.73; 95% CI 0.53, 1.00) [6]. However, this study did not control for personal smoking in analyses, and the authors speculated that the passive smoking association was likely explained by a correlation between parental smoking and personal smoking. While our risk estimate size for home exposure during childhood (OR = 0.86) is consistent with these pooled analysis results, we did not find a dose-response with greater intensity-years of passive smoke exposure at home during childhood increasing PD risk(p-trend = 0.63).

The extensive exposure data collected in the CTS provided an opportunity to investigate the relationship between passive smoking and PD in greater detail than was available in previously published epidemiologic studies, particularly cohort studies. We distinguished between exposures in three different settings and estimated exposure effects for one setting while controlling for all others. Data collected by age period allowed us to consider timing of passive smoke exposure during different decades of life prior to PD onset. In addition to the setting and timing of passive smoke exposure, we examined exposure intensity and duration semi-quantitatively, using cumulative measures of duration of years of exposure, intensity of exposure, and a combined duration-intensity measure. Results did not support overall exposure-response relationships and thus did not reinforce the notion that passive smoking is negatively associated with PD risk. It is possible that exposure at home during adulthood is inversely associated with PD risk; however, this finding was contrary to the results for other social settings, especially in young adulthood.

Tobacco and tobacco smoke contain nicotine, which has been shown to stimulate dopaminergic neurons, provide relief of parkinsonian symptoms and inhibit formation of α-synuclein fibrils in-vitro [27,28]. Tobacco smoke also contains components that inhibit the monoamine oxidase B enzyme, which may slow clinical disease progression in PD [29]. It could be argued that the dose of passive smoke in our study was too low to have any biological effect. However, a previous study in the CTS found elevated risks of invasive breast cancer with passive smoke exposure of more than 30 years, exposure of high intensity(>3) and at high intensity-years(i.e., >42) [22]. Our categories of duration, intensity and intensity-years overlap with those for which positive breast cancer effects were estimated; this might argue against the possibility that the exposures in our study reflect a sub-threshold dose at least in terms of possible carcinogenicity.

To our knowledge, we are the first to examine PD risk in association with passive smoke exposure in social settings other than the home or work place. There are several possible explanations for the results we observed. The “other” setting item asked about non-home, non-work settings such as those with friends, commuting or other social settings, and is relatively open-ended. It is unlikely that exposure in the social setting would have been systematically reported differently by PD cases and non-cases within this cohort. Data on passive smoking and PD were collected prospectively in the CTS; the questionnaire with passive smoking items preceded the PD self-report by eight years. Since the association for the other/social setting was driven by exposure during the 20's and 30's, and these results are not consistent with those for this age period and other settings, rather than suggesting an age-specific effect of passive smoke exposure on PD risk for one specific setting, this may be a spurious finding due to the many subgroup analyses in a relatively small set of never smoking PD patients.

The study population was comprised of predominantly white women who are college educated, public school teachers and administrators in California and who have low rates of personal smoking that made studying passive smoking in non-smokers possible, but also renders our results less generalizable to other populations. Compared to the majority of previous studies, we had a larger number of PD cases, particularly incident PD cases. We validated most PD diagnoses, and used all possible information to make reasonable decisions about true disease status in those we were unable to recontact [21]. About 50% of the original CTS cohort did not respond to the follow-up survey that included the PD question. It is thus possible that the cohort included additional women with PD who were too ill at follow-up to participate. Controls were selected from the same parent cohort as the cases, and selection bias would only have occurred if cases and controls were lost to follow-up according to both disease and exposure status which would assume that passive smoke-exposed PD cases were more or less likely to drop out than matched controls. We did not have data to assess potential confounding by environmental factors such as well water exposure, or to examine potential gene-environment interactions such as for genes which have been suggested to modify the effect of nicotine from personal smoking on PD risk [30].

Taken together, our results do not convincingly support a general protective effect of passive smoking in Parkinson's disease especially considering results for intensity and duration of passive smoke exposure taken together across age periods and settings, but they suggest that setting-specific exposures may merit additional attention.

Conflict of interest

The authors have none to disclose.

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