Title

Olfaction and incident Parkinson disease in US white and black older adults.

Journal

Neurology, 89(14)

Authors

Chen, Honglei
Shrestha, Srishti
Huang, Xuemei
et al.

Publication Date

2017-10-03

DOI

10.1212/WNL.0000000000004382

Peer reviewed

Olfaction and incident Parkinson disease in US white and black older adults

Honglei Chen, MD, PhD
Srishti Shrestha, PhD
Xuemei Huang, MD, PhD
Samay Jain, MD, MS
Xuguang Guo, PhD
Gregory J. Tranah, PhD
Melissa E. Garcia, MPH
Suzanne Satterfield, MD
Caroline Phillips, MS
Tamara B. Harris, MD, PhD
For the Health ABC Study

Correspondence to Dr. Chen: hchen@epi.msu.edu

ABSTRACT

Objective: To investigate olfaction in relation to incident Parkinson disease (PD) in US white and black older adults.

Methods: The study included 1,510 white (mean age 75.6 years) and 952 black (75.4 years) participants of the Health, Aging, and Body Composition study. We evaluated the olfaction of study participants with the Brief Smell Identification Test (BSIT) in 1999–2000. We retrospectively adjudicated PD cases identified through August 31, 2012, using multiple data sources. We used multivariable Cox models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: During an average of 9.8 years of follow-up, we identified a total of 42 incident PD cases, including 30 white and 12 black participants. Overall, poor sense of smell, as indicated by a lower BSIT score, was associated with higher risk of PD. Compared with the highest tertile of BSIT (t3), the HR was 1.3 (95% CI 0.5–3.6) for the second tertile (t2) and 4.8 (95% CI 2.0–11.2) for the lowest tertile (t1) ($p_{trend} < 0.00001$). Further analyses revealed significant associations for incident PD in both the first 5 years of follow-up ($HR_{t1/[t2+t3]}$ 4.2, 95% CI 1.7–10.8) and thereafter ($HR_{t1/[t2+t3]}$ 4.1, 95% CI 1.7–9.8). This association appeared to be stronger in white ($HR_{t1/[t2+t3]}$ 4.9, 95% CI 2.3–10.5) than in black participants ($HR_{t1/[t2+t3]}$ 2.5, 95% CI 0.8–8.1), and in men ($HR_{t1/[t2+t3]}$ 5.4, 95% CI 2.3–12.9) than in women ($HR_{t1/[t2+t3]}$ 2.9, 95% CI 1.1–7.8).

Conclusions: Poor olfaction predicts PD in short and intermediate terms; the possibility of stronger associations among men and white participants warrants further investigation. ***Neurology*®** **2017;89:1441–1447**

GLOSSARY

BSIT = Brief Smell Identification Test; **CI** = confidence interval; **HAAS** = Honolulu-Asia Aging Study; **Health ABC** = Health, Aging, and Body Composition; **HR** = hazard ratio; **ICD-9-CM** = International Classification of Diseases-9-Clinical Modification; **PD** = Parkinson disease; **PRIPS** = Prospective Evaluation of Risk Factors for Idiopathic Parkinson's Syndrome.

Prospective studies clearly demonstrated that olfactory impairment is associated with a higher risk for Parkinson disease (PD).[1–4] However, these studies were almost exclusively conducted in white[1–3] or Asian populations.[4] Little is known about olfaction and PD among black patients. Such an investigation, however, would be intriguing, because black patients are more likely to have poor sense of smell than white patients,[5] yet they may be less likely to have PD.[6,7] Equally interesting is a potential sex difference in the sense of smell observed in cross-sectional studies.[8] In addition, few studies have examined the temporal relationship. For example, the Honolulu-Asia Aging Study (HAAS) suggests that poor sense of smell only predicts short-term PD diagnosis within 4 years.[4] We therefore evaluated the sense of smell in relation to incident PD among 1,510 white and 952 black participants of the Health, Aging, and Body Composition (Health ABC) study overall, and by race, sex, and the length of follow-up.

Editorial, page 1432

Supplemental data at Neurology.org

From the Epidemiology Branch (H.C., S. Shrestha), National Institute of Environmental Health Sciences, Research Triangle Park, NC; Department of Epidemiology and Biostatistics (H.C.), College of Human Medicine, Michigan State University, East Lansing; Department of Neurology (X.H.), Pennsylvania State University College of Medicine, Hershey; Department of Neurology (S.J.), University of Pittsburgh School of Medicine, PA; Westat Inc. (X.G.), Durham, NC; California Pacific Medical Center Research Institute (G.J.T.), San Francisco; Laboratory of Epidemiology, Demography, and Biometry (M.E.G., C.P., T.B.H.), National Institute on Aging, Bethesda, MD; and Department of Preventive Medicine (S. Satterfield), University of Tennessee Health Science Center, Memphis. M.E.G. is currently affiliated with the National Heart, Lung, and Blood Institute, Bethesda, MD.

Coinvestigators are listed at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

METHODS

Study population. The Health ABC is a prospective study designed to investigate if changes in body composition act as a common pathway by which multiple diseases affect morbidity, disability, and mortality in community-dwelling older adults.[9] Details of the study were published previously.[9] Briefly, in 1997–1998, the study enrolled 3,075 well-functioning community-dwelling individuals (48.4% men and 41.6% black participants) aged 70–79 years in the metropolitan areas of Pittsburgh, Pennsylvania, and Memphis, Tennessee. The cohort followed study participants with annual clinical or home visits through year 6 and then in years 8, 10, 11, and 16. Interviewers called study participants to update contact and health status every 6 months between enrollment and year 15 and then quarterly through year 17. The cohort evaluated the sense of smell of 2,544 study participants at the year 3 clinical examination in 1999–2000 (hereafter referred as baseline) with the 12-item Brief Smell Identification Test (BSIT; Sensonics, Haddon Heights, NJ).[10] After excluding 49 participants without a valid BSIT score, 19 prevalent PD cases diagnosed before or in the baseline year, and 14 participants who were censored in the baseline year, the current analyses included 2,462 participants (1,510 white and 952 black participants). We followed eligible participants from baseline until the date of PD diagnosis, death, last contact, or August 31, 2012, whichever came first.

Standard protocol approvals, registrations, and patient consents. The Health ABC Study protocol was approved by the institutional review boards at the University of Pittsburgh, the University of Tennessee, and the University of California–San Francisco. All participants signed informed consent at enrollment.

PD ascertainment. We identified potential PD cases from multiple data sources. At the clinical visits of years 1, 2, 3, and 5, the study asked participants to show all medications that they used in the last 2 weeks and, for each medication, to report the name, dose, and frequency of use, reason for use, and year of first use. In years 8, 10, and 11, the study asked participants to report medication use in the last 30 days, including name, current use, frequency of use, and duration of use (years 8 and 10). The study also queried about physician diagnosis of PD at enrollment and in a substudy at year 13. In addition, the study conducted comprehensive hospitalization and death surveillance. For each hospitalization, up to 20 diagnoses were summarized on the discharge form according to the ICD-9-CM. This discharge summary, along with records of medical history and physical examinations, was subsequently reviewed by a local event adjudicator, and diseases presented at the hospitalization were adjudicated. For each death event, the cohort conducted an exit interview with a knowledgeable proxy who provided information on physical functioning of the study participant while alive and details of the event. These data, together with other relevant information such as recent hospitalizations, were centrally reviewed by a team of experts and the underlying cause of death was adjudicated by consensus. At the time of the present study, hospitalization and death surveillances were complete through August 2012.

Based on these follow-up data, we conducted a retrospective case adjudication in 2015. We first identified potential PD cases that met at least one of the following: (1) use of antiparkinsonian medications (carbidopa/levodopa, dopamine agonists, monoamine oxidase B inhibitors, amantadine, or anticholinergic drugs) at any of the medication surveys; (2) self-reported PD diagnosis; (3) local adjudication of PD as the cause of hospitalization or ICD-9 code of PD (332.0) on the discharge form; and (4) PD as the centrally adjudicated cause of death or reported on the proxy interview following death. From these sources, we identified a total of 156 potential PD cases. For each potential patient, we prepared a spreadsheet that included the aforementioned data as well as complete sets of medication and hospitalization data that were collected during the follow-up. Two experienced movement disorder specialists (X.H. and S.J.) independently reviewed these data and comprehensively considered the number of sources that indicated a PD diagnosis, internal consistency, and evidence against PD diagnosis. Examples of internal consistency include reporting PD medications in multiple years, reporting PD as the reason for taking the medication, or local adjudication of PD as the reason for multiple hospitalizations. Examples of contradictory evidence include neuroleptic use before PD medication, reporting restless leg syndrome as the reason for taking PD medication, or use of dementia medication or hospitalization with dementia prior to or at first evidence of PD. We defined PD cases as (1) 2 independent sources of PD identification without any contradictory evidence (n = 58) or (2) only 1 source of PD identification with clear internal consistency and no evidence against PD (n = 13). As hospitalization and death became the only sources to identify potential PD cases after the last medication survey, we also included potential cases whose only source of information was from adjudicated hospitalization (n = 7) or death (n = 3) after the last available medication survey. We finally adjudicated a total of 81 potential PD cases. We further defined the year of diagnosis as the first year that PD medication (n = 48) or diagnosis (n = 1) was reported. If PD was first identified by hospitalization (n = 29) or death (n = 3), we defined year of diagnosis as the middle point of first identification and the previous year of medical survey without reports of PD medication use. After excluding 19 prevalent cases (i.e., diagnosed before or in year 3) and 20 cases without BSIT scores, we had 42 incident PD cases for the current analysis.

The Brief Smell Identification Test. The BSIT is a short version of the 40-item Pennsylvania Smell Identification Test and has been widely used in clinical and epidemiologic studies.[4,11] The test asks participants to scratch and smell 12 daily odorants, one at a time, and to identify the correct odorant from 4 possible answers in a multiple choice format. One point was given for each correct answer with a total score ranging from 0 to 12 with a higher score indicating a better sense of smell.[10] We excluded 49 participants with >3 missing items from the analyses and prorated for other incompletes (93 with 1, 29 with 2, and 10 with 3 missing) according to their actual score based on completed items. For example, if a participant completed 10 items and 9 were correct, the total prorated BSIT score would be 10.8. The BSIT also includes a question about history of head injury defined as "hit in the head hard enough to make you faint."

Assessment of covariates. The study also collected information on demographics (i.e., age, sex, race, and education), lifestyle (i.e., smoking and coffee drinking), and general health status via structured face-to-face interviews as part of its clinical visits. With the exception of coffee consumption, which was asked at year 2 as part of a food frequency questionnaire, other covariates corresponded to the same year of the sense of smell test.

Statistical analysis. We first conducted analyses with all participants and then separately by race, sex, and length of follow-up (the first 5 years and thereafter). In the primary analysis, we categorized the sense of smell into tertiles, with the highest tertile (t3, better olfaction) as reference. We used multivariable Cox models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) with age as the time scale and left-truncation on age at year 3, first adjusting for race and sex when appropriate and

Table 1 Baseline population characteristics according to the Brief Smell Identification Test (BSIT) score (n = 2,462)

	BSIT score tertiles (olfaction)		
	Tertile 3 (better)	Tertile 2 (good)	Tertile 1 (poor)
BSIT score range	11–12	9–10	0–8
No.	835	863	764
Age, y, mean ± SD[a]	75.1 ± 2.6	75.6 ± 2.9	76.1 ± 2.9
Men, %[a]	38.2	48.3	59.0
Black, %[a]	31.0	38.7	47.0
Study site, %[b]			
Memphis	44.4	49.7	52.2
Pittsburgh	55.6	50.3	47.8
Education, %[a]			
Below high school	14.9	21.3	31.9
High school	33.9	34.9	29.7
Post high school	51.3	43.5	38.0
Missing	0.0	0.3	0.4
Smoking status, %[a]			
Never	49.6	43.1	41.6
Past	45.5	49.0	47.5
Current	4.9	7.6	10.7
Missing	0.0	0.2	0.1
Coffee, cups/d, %			
None	21.7	24.7	27.0
<1	14.1	12.5	12.4
1–1.9	26.1	23.9	27.5
≥2	38.1	38.9	33.1
General health, %[a]			
Excellent/very good	50.3	44.5	39.7
Good	34.6	40.0	37.3
Fair/poor	15.1	15.4	22.9
Missing	0.0	0.1	0.1
Head injury, %			
No	91.6	90.2	88.5
Yes	8.3	9.7	11.4
Missing	0.1	0.1	0.1

The p values were obtained from χ^2 test except for age, for which analysis of variance was used.
[a] $p < 0.001$.
[b] $p < 0.01$.

then additionally for other potential confounders. We also tested statistical interactions of the sense of smell with sex or race on PD risk by including a 2-way cross-product term in regression models. In all stratified analyses, we combined the highest 2 tertiles (t2+t3) of BSIT score as the reference due to sample size considerations. We conducted power analyses using PS-Power and Sample Size Calculation (biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize). With our sample sizes, we had adequate statistical power ($\beta = 80\%$) to detect a $HR_{t1/[t2+t3]} \geq 2.8$ in white participants, ≥5.1 in black participants, ≥3.0 in men, and ≥4.0 in women.

To further explore the temporal relationship of poor sense of smell with incident PD, we conducted 2 additional analyses: (1) with incident cases, a series of lagged analyses by excluding the first years of follow-up with 1-year increment until year 6; (2) cross-sectional analyses with prevalent PD cases (n = 19) diagnosed before or at year 3 using logistic regression models. We conducted all statistical analyses with SAS version 9.3 (SAS Systems Inc., Cary, NC) and a 2-sided α of 0.05.

RESULTS During an average of 9.8 years of follow-up, we identified 42 incident PD cases, including 30 white and 12 black participants. The incidence of PD per 100,000 person-years was 174 overall, 197 in white participants, 135 in black participants, 235 in men, and 122 in women.

Compared with participants in the highest tertile of BSIT score (t3, better olfaction), those in the lowest tertile (t1, poor olfaction) were older and were more likely to be male, black, current smokers, and from the Memphis site (table 1). Further, they were less likely to report post high school education or optimal health status. Participants with poor sense of smell also tended to report less coffee drinking and a history of head injury, although the differences were not statistically significant. Table e-1 at Neurology.org shows associations of these covariates with incident PD. The statistical power of these analyses was limited.

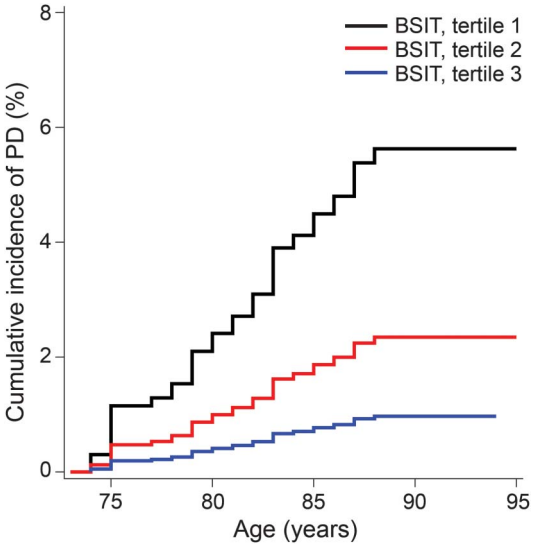
As expected, poor olfaction predicted a higher risk of PD (figure and table 2). The associations did not materially change after further adjustment for study site, education, smoking, coffee drinking, general health status, and history of head injury.

Poor sense of smell was clearly associated with higher PD risk in white participants (table 3); a similar association was suggested for black participants but it was not statistically significant. Differential associations were also suggested for sex, with an apparently stronger association in men. The interaction term for sex or race with BSIT score was not statistically significant, possibly due to small sample size. In the analysis stratified by the length of follow-up, we found significant associations for both the first 5 years of follow-up and afterwards.

In the series of lagged analyses that excluded the first years of follow-up (table 4), the association remained at similar strength ($HR_{t1/[t2+t3]}$, range 4.1–5.0) for the first 6 years of follow-up and then the HR decreased to 2.9. The corresponding odds ratio for association with prevalent cases was 7.6. Therefore, the strongest association was found with prevalent cases followed by cases diagnosed in the 6 years following the BSIT test. Data indicated moderate association beyond 6 years, but the risk estimate was less stable due to smaller sample size.

DISCUSSION In this study, we found that a single evaluation of the sense of smell was associated with

Figure Cumulative incidence of Parkinson disease (PD) by tertiles of the Brief Smell Identification Test (BSIT) score



PD risk beyond the first several years of follow-up. The association was attenuated with longer follow-up, however. Further, our data indicate that the association may be stronger in white participants and in men.

Although the Braak hypothesis is somewhat controversial,[12,13] it implies that olfactory impairment is among the early symptoms in prodromal PD. Consistently, clinical studies have identified poor sense of smell as the most sensitive nonmotor symptom in differentiating patients with newly diagnosed PD from controls.[8,14] Further, prospective follow-up of individuals with unexplained olfactory dysfunction showed much higher than expected PD conversion rate.[2,3] In addition, a case-control study in Germany found that 38.7% of patients with PD reported olfactory dysfunction on average 11.2 ± 11.1 years prior to PD diagnosis.[15]

A few population-based prospective studies also examined olfactory dysfunction in relation to PD risk. The HAAS followed 2,267 Japanese American men in Honolulu, Hawaii, for 8 years and identified 35 PD cases.[4] The study reported that men in the lowest quartile of the sense of smell score were about 5.2 (95% CI 1.5–25.6) times more likely to receive a PD diagnosis than those in the highest 2 quartiles in the first 4 years after olfaction assessment (n = 19 cases).[4] However, the authors did not identify a higher risk for the second 4 years of follow-up (n = 16 cases, corresponding HR 0.3, 95% CI 0–2.7).[4] Recently, several cohort studies have been initiated in the United States and Europe to specifically examine sense of smell and other markers as predictors of future PD in the general population.[1,16,17] For example, the Prospective Evaluation of Risk Factors for Idiopathic Parkinson's Syndrome (PRIPS) study (n = 1,847)[18] reported preliminary findings for the first 3 years and for years 3–5 of follow-up. In each follow-up period, 10 patients with PD were identified and 6 (60%) had reduced sense of smell at baseline, as compared to 28.8% among individuals free of PD.[18]

Based on this and other evidence, olfactory dysfunction was recently proposed as part of the criteria for prodromal PD.[19] However, its potential usefulness as a screening tool for prodromal or undiagnosed PD in the general population awaits further investigations, in part because of the low PD incidence, the lack of specificity of olfactory dysfunction to PD, and the lack of understanding of temporal relationship of olfactory dysfunction with PD.[20] Future research on the pathogenesis of olfactory dysfunction in the context of PD development and its manifestation pattern in combination with other key prodromal symptoms, biomarkers, or risk factors may help evaluate its potential to screen for prodromal PD in high-risk populations.

Compared with previous population-based prospective studies, the current study has longer follow-up and showed that poor olfaction was associated with PD beyond the first several years of follow-up, although the association was somewhat attenuated. Another important strength of the current study is the inclusion of both white and black participants. Data on PD in black participants are limited, but evidence indicates possibly lower PD incidence than in

Table 2 Tertiles of the Brief Smell Identification Test score and the risk for Parkinson disease

			Hazard ratios (95% confidence intervals)	
	Person-years	No. of cases	Model 1[a]	Model 2[b]
Tertile 3	8,752	7	1.0 (Ref.)	1.0 (Ref.)
Tertile 2	8,596	9	1.3 (0.5–3.6)	1.4 (0.5–3.8)
Tertile 1	6,772	26	4.8 (2.0–11.2)	5.1 (2.1–11.9)
p for trend			0.00001	0.00001

[a] Model 1: age is the time scale, adjusting for sex and race.
[b] Model 2: further adjusted for study site, education, smoking, caffeine intake, general health status, and history of head injury.

Table 3 Tertiles of the Brief Smell Identification Test score and risk for Parkinson disease by race, sex, and length of follow-up

	White			Black		
	Person-years	No. of cases	HR (95% CI)[a]	Person-years	No. of cases	HR (95% CI)[a]
Tertiles 2 + 3	11,498	11	1.0 (Ref.)	5,850	5	1.0 (Ref.)
Tertile 1	3,714	19	4.9 (2.3–10.5)	3,058	7	2.5 (0.8–8.1)
p for interaction						0.3
	Men			Women		
	Person-years	No. of cases	HR (95% CI)[a]	Person-years	No. of cases	HR (95% CI)[a]
Tertiles 2 + 3	7,198	7	1.0 (Ref.)	10,150	9	1.0 (Ref.)
Tertile 1	3,850	19	5.4 (2.3–12.9)	2,922	7	2.9 (1.1–7.8)
p for interaction						0.4
	First 5 years of follow-up			After the first 5 years of follow-up		
	Person-years	No. of cases	HR (95% CI)[a]	Person-years	No. of cases	HR (95% CI)[a]
Tertiles 2 + 3	8,386	7	1.0 (Ref.)	8,962	9	1.0 (Ref.)
Tertile 1	3,635	13	4.2 (1.7–10.8)	3,137	13	4.1 (1.7–9.8)

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Based on Cox regression model with age as the time scale, adjusting for sex or race.

white participants.[6,7] Notably, data also suggest that older black participants are more likely to have poor sense of smell than white participants.[5] If both observations are true, one may speculate that a poor sense of smell may not be as strong a predictor for PD in black as in white patients. Data from the current study seem to support this possibility. Reasons for this potential racial difference are unclear. One possibility is that, compared to white participants, the etiology of olfactory dysfunction in black participants is more diverse and complex, and that PD-related pathology is a relatively minor contributor. Alternatively, one may argue that the BSIT test performs better in white than in black older adults. Although BSIT was designed to be used across different cultures,[10] we could not exclude this possibility.

Investigations into a potential sex difference in the relationship between olfaction and PD are equally interesting. Sex differences have been documented for PD incidence[6] and risk factors,[21,22] as well as clinical presentation.[23,24] Further, many studies found that men had poorer olfaction than women, and this is true for both patients with PD[8] and the general elderly population.[5,25] The HAAS included men only[4] and the PRIPS had only 21 cases, which precluded sex-specific analyses.[18] In the current study, poor

Table 4 Tertiles of the Brief Smell Identification Test score in relation to prevalent and incident Parkinson disease with lag analyses

			Incident cases[b]					
	Prevalent cases[a]		All cases		1-Year lag		2-Year lag	
	No. of cases	OR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)
Tertiles 2 + 3	5	1.0 (Ref.)	16	1.0 (Ref.)	16	1.0 (Ref.)	12	1.0 (Ref.)
Tertile 1	14	7.6 (2.7–21.5)	26	4.1 (2.2–7.7)	26	4.2 (2.2–7.9)	24	5.0 (2.5–10.2)
	Incident cases[b]							
	3-Year lag		4-Year lag		5-Year lag		6-Year lag	
	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)
Tertiles 2 + 3	10	1.0 (Ref.)	10	1.0 (Ref.)	9	1.0 (Ref.)	7	1.0 (Ref.)
Tertile 1	17	4.4 (2.0–9.7)	15	4.1 (1.8–9.3)	13	4.2 (1.7–9.9)	7	2.9 (1.0–8.4)

Abbreviations: CI = confidence interval; HR = hazard ratio; OR = odds ratio.
[a] Analysis of prevalent cases using logistic regression adjusting for age, sex, and race.
[b] Analysis of incident cases using Cox regression model with age as the time scale, adjusting for sex and race; lagged analyses were conducted by excluding the first years of follow-up with 1-year increment up to 6 years.

olfaction was statistically associated with higher PD risk in both men and women. However, the strength of the association was twice as strong in men, indicating that poor sense of smell may be a better predictor of PD in men than in women.

The study has several notable limitations. First, although the cohort's data collection was prospective, PD case adjudication was performed retrospectively at the end of the follow-up. As PD may take years to be diagnosed, without active and systematic case ascertainment, we might have inadvertently missed some cases and adjudication errors were also possible. Second, despite our due diligence in estimating the date of first evidence for a PD diagnosis, this information remained imprecise. In particular, some of the prevalent cases at baseline might have been mistakenly adjudicated as incident cases in the first several years of follow-up. For these reasons, interpretation of our results on the temporal relationship requires caution. Future studies with active case confirmation and more accurate documentation of date of PD diagnosis are needed. Third, the sense of smell is more than smell identification and olfactory dysfunction could be due to many reasons other than neurodegeneration (e.g., chronic rhinosinusitis).[26] The current study only tested smell identification and did not evaluate other potential causes for olfactory dysfunction. Fourth, the loss of the sense of smell in prodromal PD may be gradual over many years; however, available studies, including ours, measured the sense of smell only at one time point. Future studies with repeated measurements over a longer period may help better characterize the temporal relationship of olfactory dysfunction with PD. Fifth, by design, the study participants were relatively healthy and 70 years or older at enrollment, therefore the results may not be readily generalizable to younger populations. Finally, the numbers of PD cases were small, particularly for stratified analyses in women and black participants as well as for the lagged analyses. Therefore, cautious interpretations of these results are needed. Future studies should confirm our findings and investigate potential applications to clinical and etiologic research of PD.

AUTHOR CONTRIBUTIONS

Honglei Chen: study concepts/design, data acquisition, data analysis/interpretation, statistical analysis, manuscript drafting, manuscript editing, manuscript final approval, guarantor of integrity of entire study. Srishti Shrestha: data analysis/interpretation, statistical analysis, manuscript drafting, manuscript editing, manuscript final approval. Xuemei Huang: data acquisition, manuscript editing, manuscript final approval. Samay Jain: data acquisition, manuscript editing, manuscript final approval. Xuguang Guo: data analysis/interpretation, statistical analysis, manuscript editing, manuscript final approval. Gregory J. Tranah: data acquisition, data analysis/interpretation, manuscript editing, manuscript final approval. Melissa E. Garcia: data acquisition, data analysis/interpretation, manuscript editing, manuscript final approval. Suzanne Satterfield, data acquisition, data analysis/interpretation, manuscript editing, manuscript final approval. Caroline Phillips: data acquisition, data analysis/interpretation, manuscript editing, manuscript final approval. Tamara B. Harris: study concepts/design, data acquisition, data analysis/interpretation, manuscript editing, manuscript final approval.

ACKNOWLEDGMENT

Additional information: Coauthor Samay Jain, MD, MS, died September 8, 2016. Coauthor Suzanne Satterfield, MD, died January 15, 2017.

STUDY FUNDING

The study was supported by the National Institute on Aging (NIA) contracts N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106; NIA grant R01-AG028050 and National Institute of Nursing Research grant R01-NR12459; and the Intramural Research Program of the NIH, the National Institute of Environmental Health Sciences (Z01 ES101986), and NIA. Dr. Xuemei Huang is supported in part by the National Institute of Neurologic Disorders and Stroke (NS060722 and NS082151). This manuscript does not reflect the official view of the NIH.

DISCLOSURE

H. Chen serves on the editorial boards of the *American Journal of Epidemiology*, *International Journal of Molecular Epidemiology and Genetics*, and *American Journal of Neurodegenerative Disease*. S. Shrestha, X. Huang, S. Jain, X. Guo, G. Tranah, M. Garcia, S. Satterfield, C. Phillips, and T. Harris report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received October 4, 2016. Accepted in final form April 20, 2017.

REFERENCES

1. Berg D, Godau J, Seppi K, et al. The PRIPS study: screening battery for subjects at risk for Parkinson's disease. Eur J Neurol 2013;20:102–108.
2. Haehner A, Hummel T, Hummel C, Sommer U, Junghanns S, Reichmann H. Olfactory loss may be a first sign of idiopathic Parkinson's disease. Mov Disord 2007;22:839–842.
3. Ponsen MM, Stoffers D, Booij J, van Eck-Smit BL, Wolters E, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol 2004;56:173–181.
4. Ross GW, Petrovitch H, Abbott RD, et al. Association of olfactory dysfunction with risk for future Parkinson's disease. Ann Neurol 2008;63:167–173.
5. Pinto JM, Schumm LP, Wroblewski KE, Kern DW, McClintock MK. Racial disparities in olfactory loss among older adults in the United States. J Gerontol A Biol Sci Med Sci 2014;69:323–329.
6. Van Den Eeden SK, Tanner CM, Bernstein AL, et al. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol 2003;157:1015–1022.
7. Wright Willis A, Evanoff BA, Lian M, Criswell SR, Racette BA. Geographic and ethnic variation in Parkinson disease: a population-based study of US Medicare beneficiaries. Neuroepidemiology 2010;34:143–151.
8. Liu R, Umbach DM, Peddada SD, et al. Potential sex differences in nonmotor symptoms in early drug-naive Parkinson disease. Neurology 2015;84:2107–2115.
9. Simonsick EM, Newman AB, Nevitt MC, et al. Measuring higher level physical function in well-functioning older adults: expanding familiar approaches in the Health ABC study. J Gerontol A Biol Sci Med Sci 2001;56:M644–M649.
10. Doty RL, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). Laryngoscope 1996;106:353–356.
11. Double KL, Rowe DB, Hayes M, et al. Identifying the pattern of olfactory deficits in Parkinson disease using the Brief Smell Identification Test. Arch Neurol 2003;60:545–549.

12. Dickson DW, Uchikado H, Fujishiro H, Tsuboi Y. Evidence in favor of Braak staging of Parkinson's disease. Mov Disord 2010;25(suppl 1):S78–S82.
13. Burke RE, Dauer WT, Vonsattel JP. A critical evaluation of the Braak staging scheme for Parkinson's disease. Ann Neurol 2008;64:485–491.
14. Nalls MA, McLean CY, Rick J, et al. Diagnosis of Parkinson's disease on the basis of clinical and genetic classification: a population-based modelling study. Lancet Neurol 2015;14:1002–1009.
15. Gaenslen A, Swid I, Liepelt-Scarfone I, Godau J, Berg D. The patients' perception of prodromal symptoms before the initial diagnosis of Parkinson's disease. Mov Disord 2011;26:653–658.
16. Siderowf A, Jennings D, Eberly S, et al. Impaired olfaction and other prodromal features in the Parkinson At-Risk Syndrome Study. Mov Disord 2012;27:406–412.
17. Gaenslen A, Wurster I, Brockmann K, et al. Prodromal features for Parkinson's disease: baseline data from the TREND study. Eur J Neurol 2014;21:766–772.
18. Lerche S, Seppi K, Behnke S, et al. Risk factors and prodromal markers and the development of Parkinson's disease. J Neurol 2014;261:180–187.
19. Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord 2015;30:1600–1611.
20. Heinzel S, Roeben B, Ben-Shlomo Y, et al. Prodromal markers in Parkinson's disease: limitations in longitudinal studies and lessons learned. Front Aging Neurosci 2016;8:147.
21. Gao X, O'Reilly EJ, Schwarzschild MA, Ascherio A. Prospective study of plasma urate and risk of Parkinson disease in men and women. Neurology 2016;86:520–526.
22. 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.
23. Miller IN, Cronin-Golomb A. Gender differences in Parkinson's disease: clinical characteristics and cognition. Mov Disord 2010;25:2695–2703.
24. Haaxma CA, Bloem BR, Borm GF, et al. Gender differences in Parkinson's disease. J Neurol Neurosurg Psychiatry 2007;78:819–824.
25. Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. JAMA 2002;288:2307–2312.
26. Doty RL. The olfactory system and its disorders. Semin Neurol 2009;29:74–81.