Title
Olfaction and risk of dementia in a biracial cohort of older adults.

Journal
Neurology, 88(5)

Authors
Freimer, Daniel
Chen, Honglei
Asao, Keiko
et al.

Publication Date
2017-01-31

DOI
10.1212/WNL.0000000000003558

Peer reviewed

Olfaction and risk of dementia in a biracial cohort of older adults

Kristine Yaffe, MD
Daniel Freimer, BA
Honglei Chen, MD, PhD
Keiko Asao, MD, MPH, PhD
Andrea Rosso, MPH, PhD
Susan Rubin, MPH
Greg Tranah, PhD
Steve Cummings, MD
Eleanor Simonsick, PhD

Correspondence to Dr. Yaffe: kristine.yaffe@ucsf.edu

ABSTRACT

Objective: Prior studies indicate that olfactory function may be an early marker for cognitive impairment, but the body of evidence has been largely restricted to white populations.

Methods: We studied 2,428 community-dwelling black and white older adults (baseline age 70–79 years) without dementia enrolled in the Health, Aging, and Body Composition (Health ABC) study. Olfaction was measured as odor identification (OI) with the 12-item Cross Cultural Smell Identification Test in year 3. We defined incident dementia over 12 years on the basis of hospitalization records, prescription for dementia medication, or 1.5-SD decline in race-stratified global cognition score. We assessed dementia risk associated with OI score (by tertile) using Cox proportional hazards models. All analyses were stratified by race.

Results: Poorer OI in older adults without dementia was associated with increased risk of dementia. After adjustment for demographics, medical comorbidities, and lifestyle characteristics, white participants in the poor or moderate OI tertile had greater risk of dementia (adjusted hazard ratio [HR] 3.34, 95% confidence interval [CI] 2.45–4.54; and HR 1.84, 95% CI 1.33–2.54, respectively) compared to those in the good tertile of function. Among blacks, worse OI was associated with an increased risk of dementia, but the magnitude of the effect was weaker (p for interaction = 0.04) for the poor OI tertile (adjusted HR 2.03, 95% CI 1.44–2.84) and for the moderate tertile (adjusted HR 1.42, 95% CI 0.97–2.10). There was no interaction between OI and *APOE* ε4 and risk of dementia.

Conclusions: While the magnitude of the association was stronger in whites, we found that poor OI was associated with increased risk of dementia among both black and white older adults.
Neurology® 2017;88:456–462

GLOSSARY

AD = Alzheimer disease; **BMI** = body mass index; **CI** = confidence interval; **B-SIT** = Cross Cultural Smell Identification Test; **Health ABC** = Health, Aging, and Body Composition; **HR** = hazard ratio; **OI** = odor identification; **3 MS** = Modified Mini-Mental Status Examination.

Olfactory testing may be a simple, inexpensive, and highly sensitive method of identifying older adults at risk for developing dementia, particularly when combined with other early markers.[1–3] While it is well established that olfactory deficits are present in symptomatic Alzheimer disease (AD),[4] recent studies have demonstrated that deficits in olfactory functioning occur very early in the disease process, often preceding the onset of other clinical symptoms.[5] In addition, several studies have reported that olfactory deficits in cognitively normal older adults are associated with increased risk for cognitive decline and dementia.[6–8] Thus, olfactory testing may be a useful screen to identify risk of neurodegenerative disease. Because most previous studies have been limited to white older adults, potential race differences in the olfaction-dementia relationship remain unexplored, despite previously reported race differences in olfaction[9] and dementia risk.[10–13]

From the Departments of Psychiatry (K.Y.), Neurology (K.Y.), and Epidemiology and Biostatistics (K.Y., S.R.), University of California; San Francisco VA Medical Center (K.Y.); NCIRE–The Veterans Health Research Institute (K.Y., D.F.), San Francisco, CA; Epidemiology Branch (H.C.), National Institute of Environmental Health Sciences, Research Triangle Park, NC; Department of Preventive Medicine (K.A.), University of Tennessee Health Science Center, Memphis; Department of Epidemiology (A.R.), Graduate School of Public Health, University of Pittsburgh, PA; California Pacific Medical Center Research Institute (G.T., S.C.), San Francisco; and Translational Gerontology Branch (E.S.), National Institute on Aging, Baltimore, MD.

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.

The present study investigates the association between olfactory dysfunction and dementia risk among black and white older adults in the prospective Health, Aging, and Body Composition (Health ABC) study, a biracial cohort of older adults who were cognitively normal at baseline and followed up for dementia for more than a decade. Data in this study come from the Health ABC study. We sought to determine whether the relationship between olfaction and dementia existed in both blacks and whites and whether this relationship was modified by the presence of the *APOE* ε4 allele.

METHODS

Participants. Our cohort comprised older adults (baseline age 70–79 years) from the Health ABC study. The prospective cohort of 3,075 community-dwelling black and white older adults was recruited from a random sample of Medicare-eligible adults living within designated ZIP codes in Memphis, TN, and Pittsburgh, PA, in 1997 to 1998. To be eligible, participants had to report no difficulties performing activities of daily living, to be able to walk a quarter mile or climb 10 steps without resting, to be free from life-threatening cancers, and to plan to remain in the study area for at least 3 years.

Standard protocol approvals, registrations, and patient consents. All participants signed an informed consent form that was approved by the institutional review boards of each clinical site and the study coordinating center.[14]

Olfaction was measured in year 3 of the study and serves as the baseline for our study. We excluded individuals who had dementia at or before year 3 (n = 75), those who did not attend year 3 visit or had no follow-up after year 3 (n = 227), and those missing olfactory testing (n = 341), for a final analytic sample of 2,428 (918 black, 1,510 white, as indicated by self-report) participants. Compared to those with follow-up after year 3, participants without follow-up were more likely to be black, to be male, and to have less than high school education, lower literacy, hypertension, diabetes mellitus, myocardial infarction, and stroke ($p < 0.05$ for all).

Measures. The 12-item Cross Cultural Smell Identification Test (B-SIT), in which participants are presented with a series of 12 odorants and are asked to identify the odor among 4 possible choices, was used to assess odor identification (OI).[15] The B-SIT was computed as the sum of the correct responses for a maximum possible score of 12. On the basis of prior evidence of race disparities in OI performance,[9] we tested the distribution of OI scores and found significant differences between the 2 race groups. In the absence of standardized race-adjusted B-SIT norms, we divided the participants into race- and sex-stratified tertiles labeled good, moderate, and poor, roughly corresponding to the clinical impairment classifications used by the B-SIT: normosmic, mildly microsmic, and anosmic.[15]

Global cognition was assessed repeatedly with the Modified Mini-Mental Status Examination (3 MS),[16] a cognitive screening measure that assesses concentration, orientation, language, praxis, and immediate and delayed memory. The 3 MS has been shown to be more sensitive in detecting dementia than other cognitive screening instruments.[17] Incident dementia over 12 years of follow-up was determined if any of the following qualifications were met: record of a hospitalization with dementia listed as a primary or secondary diagnosis, a documented prescription for dementia medication, or ≥1.5-SD decline in 3 MS on the basis of repeated measures from participants' baseline through last visit compared with the mean 3 MS change exhibited by race-matched peers within the cohort.[18]

Several covariates were considered potential confounders: demographics, *APOE* ε4 allele (ε4 allele present/absent), literacy, medical comorbidities, depression, head trauma, current smoking, physical activity, and body mass index (BMI). Literacy was measured at baseline with the Rapid Estimate of Adult Literacy in Medicine test and was classified as at or above ninth grade level or less than the ninth grade level.[19] Medical comorbidities (hypertension, diabetes mellitus, myocardial infarction, stroke) were determined from a combination of self-reported data, physician diagnosis, medications, and laboratory values measured at baseline. Depression was assessed with the Centers for Epidemiologic Studies Depression scale, for which a score of ≥10 is considered indicative of high depressive symptomatology.[20] Physical activity was assessed through a structured interview about daily activities, and the number of minutes spent walking briskly was calculated. For this analysis, we have divided participants into those who typically briskly walk at least 90 min/wk and those who do not.

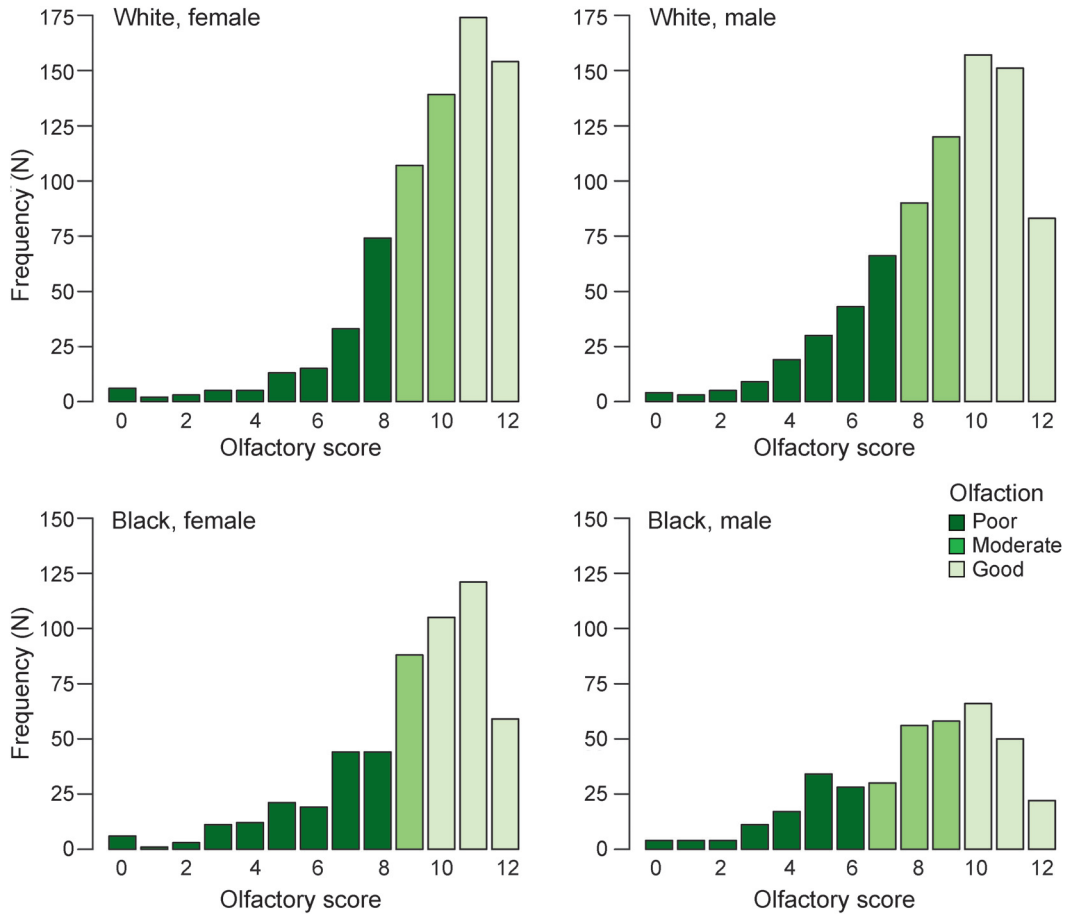
Statistical analysis. All analyses were stratified by race because of previously reported racial differences in olfaction,[9] observed differences in the distribution of OI score, and our observed interaction of race on dementia risk ($p = 0.04$). We reported frequencies/percentages and means/SDs for participant characteristics, which were tested for differences across the sequence of OI categories with trend tests. We assessed the risk of dementia associated with OI using Cox proportional hazards models. We tested the proportional hazard assumption separately in the black and white samples. We first adjusted for demographics (age, site, race, sex, education, and literacy). The model was then additionally adjusted for medical comorbidities and lifestyle characteristics that differed across olfaction ($p \leq 0.10$). We tested for potential effect modification of the relationship between OI and dementia by *APOE* ε4. All analyses were performed in SAS 9.4.

RESULTS

The distribution of OI scores by race and sex is shown in figure 1. Participants were considered to have good OI if their score was ≥11 among white women and ≥10 among men and black women; poor OI if their score was <9 among women, <8 among white men, and <7 among black men; and moderate OI if they scored between these bounds.

Among white participants, older age, lower education and literacy, having an *APOE* ε4 allele, current smoking, and lower BMI were significantly associated with poor OI (table 1). We found a similar pattern among black participants, with older age, lower education and literacy, and lower BMI significantly associated with poor OI. In contrast, among black participants, not having an *APOE* ε4 allele was associated with worse OI. Depression and physical activity were marginally associated with OI in at least one sample (black or white) and were thus included as covariates in the fully adjusted model.

Figure 1 Distribution of odor identification score by race and sex



The Kaplan-Meier plot in figure 2 shows differences in dementia incidence by OI group over 12 years of follow-up in both races. Among whites, 33.8% of participants with poor OI developed dementia compared with 10.2% of those with good OI, with an unadjusted hazard ratio (HR) of 3.83 (95% confidence interval [CI] 2.85–5.14); those in the moderate OI tertile also had an elevated risk (HR 2.09, 95% CI 1.53–2.84) compared to those with good OI (table 2). After adjustment for demographics and demographics plus comorbidities and lifestyle factors, poor OI remained associated with a >3-fold increase in risk of dementia (adjusted HR 3.34, 95% CI 2.45–4.54), and moderate OI remained associated with increased dementia risk (adjusted HR 1.84, 95% CI 1.33–2.54). We tested whether *APOE* ε4 moderated the association between OI and dementia, but there was no significant interaction ($p = 0.74$).

Among blacks, 31.9% of participants with poor OI developed dementia compared with 17.7% of those with high OI (unadjusted HR 2.22, 95% CI 1.62–3.03), and those with moderate OI had an ≈50% increased risk of dementia (unadjusted HR 1.48, 95% CI 1.53–2.84) compared to those with good OI. In fully adjusted models, poor OI remained associated with increased risk of dementia (adjusted HR 2.03, 95% CI 1.44–2.84), but moderate OI was only marginally associated (adjusted HR 1.42, 95% CI 0.97–2.10; table 2). There was no significant interaction with *APOE* ε4 in the association between OI and dementia ($p = 0.80$).

DISCUSSION In this cohort of black and white older adults without dementia, we investigated the association between olfaction as measured by OI and risk of dementia. We found differences in the distribution of OI scores between blacks and whites of both sexes, in line with previous findings that showed differences in OI decline between older whites and blacks.[9] We also found that poorer OI was associated with increased risk of dementia over 12 years among both blacks and whites. While the magnitude of the effect was stronger in whites than blacks, our results suggest that olfactory function may help identify those at risk for dementia across racial groups.

Although changes in the olfactory system occur naturally throughout the aging process,[21] olfactory dysfunction is one of the earliest and most common symptoms of neurodegenerative disease. The mechanisms underlying olfactory loss remain unclear, but

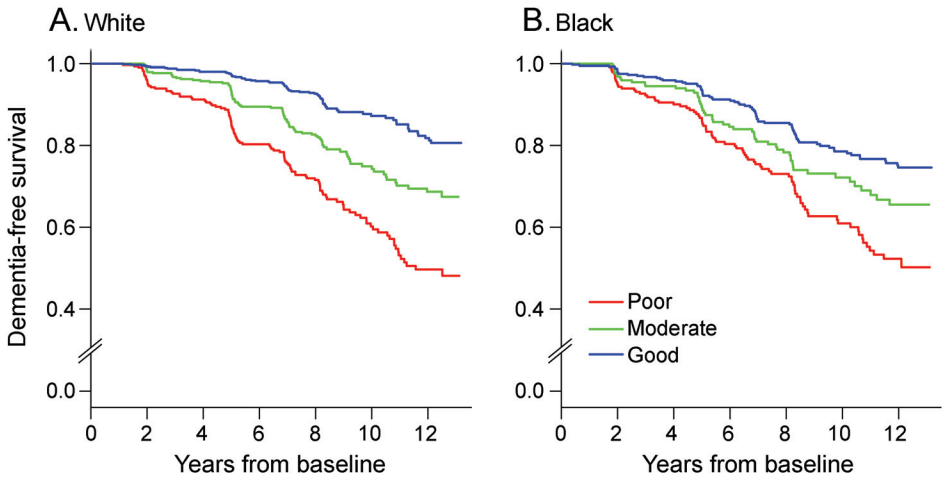
Table 1 Participant characteristics by odor identification performance

	White			
Characteristic	**Poor (n = 337)**	**Moderate (n = 455)**	**Good (n = 718)**	***p* Value**
Age, mean (SD), y	76.2 (2.8)	75.8 (2.8)	75.3 (2.8)	<0.001
Female, n (%)	156 (46.3)	247 (54.3)	327 (45.5)	0.39
Education less than high school, n (%)	46 (13.6)	58 (12.8)	69 (9.6)	0.04
Literacy less than ninth grade, N (%)	50 (14.8)	57 (12.5)	58 (8.1)	<0.001
APOE ε4 allele, n (%)	88 (27.7)	106 (24.5)	146 (21.2)	0.02
Hypertension, n (%)	231 (68.5)	330 (72.5)	497 (69.2)	0.95
Diabetes mellitus, n (%)	54 (16)	71 (15.6)	117 (16.3)	0.86
Stroke, n (%)	27 (8.1)	43 (9.5)	61 (8.6)	0.91
Head trauma, n (%)	42 (12.5)	43 (9.5)	69 (9.6)	0.20
Depression, n (%)	30 (8.9)	53 (11.6)	59 (8.2)	0.45
Current smoking, n (%)	22 (6.5)	24 (5.3)	24 (3.3)	0.02
Physical activity, n (%)	37 (11)	52 (11.4)	103 (14.4)	0.09
BMI, mean (SD), kg/m^2	25.9 (4.3)	26.4 (4.3)	26.8 (4.0)	<0.01
	Black			
Characteristic	**Poor (n = 263)**	**Moderate (n = 232)**	**Good (n = 423)**	***p* Value**
Age, mean (SD), y	76.0 (3.0)	75.5 (2.8)	75.0 (2.6)	<0.001
Female, n (%)	161 (61.2)	88 (37.9)	285 (67.4)	0.01
Education less than high school, n (%)	124 (47.3)	110 (47.8)	128 (30.3)	0.04
Literacy less than ninth grade, n (%)	149 (56.7)	116 (50.0)	144 (34.0)	<0.001
APOE ε4 allele, n (%)	78 (31.7)	65 (30.8)	154 (39.1)	<0.001
Hypertension, n (%)	218 (82.9)	194 (83.6)	352 (83.2)	0.93
Diabetes mellitus, n (%)	72 (27.4)	63 (27.3)	118 (27.9)	0.87
Stroke, n (%)	27 (10.5)	28 (12.3)	41 (9.7)	0.68
Head trauma, n (%)	23 (8.7)	25 (10.8)	29 (6.9)	0.30
Depression, n (%)	47 (17.9)	41 (17.7)	57 (13.5)	0.10
Current smoking, n (%)	40 (15.2)	28 (12.1)	43 (10.2)	0.05
Physical activity, n (%)	14 (5.3)	13 (5.6)	28 (6.6)	0.47
BMI, mean (SD), kg/m^2	28.0 (5.4)	27.9 (5.1)	29.0 (5.5)	0.02

Abbreviation: BMI = body mass index.

olfactory deficits have been shown to occur before the emergence of full clinical symptoms,[5,22,23] providing an invaluable window into neuropathologic processes during the clinically silent phase of neurodegenerative disease. Evidence suggests that one of the earliest events in the AD-related degenerative process is involvement of the olfactory bulb and tract.[24] Olfactory bulb concentrations of tau, β-amyloid, and α-synuclein have been shown to significantly increase with the Braak stages,[3] and the degree of tau, β-amyloid, and α-synuclein pathology in the olfactory bulb has been shown to reflect the degree of respective pathologies in other brain regions,[25] suggesting a potential role for olfactory testing as a severity and progression marker in AD.[4] Deficits in OI precede impairment on olfactory threshold detection tasks[26] and remain after cognitive measures and odor detection deficits are controlled for,[5] suggesting a pathophysiologic process that originates near the central olfactory structures in the medial temporal lobe.[5,23,27–29] Although the exact inception point of AD pathology in the olfactory system remains unknown, the disease course progressively involves[29] multiple levels of the olfactory system,[27,30] including peripheral structures such as the olfactory bulb and epithelium, as well as higher order olfactory pathways connected to cognitive processes.[25] Studies have shown greater OI deficits in patients with AD compared to those with vascular dementia,[31,32] suggesting that the site of vascular pathology may determine the type and severity of olfactory deficit,[33] with specific olfactory deficits observed only in patients whose corresponding

Figure 2 Kaplan-Meier plot of dementia-free survival by odor identification performance among 1,510 white (A) and 918 black (B) participants



olfactory structures sustained vascular damage, in contrast to the multiple-level impairment observed across the olfactory system in AD pathology.[25,27,30] Because we did not have detailed information on dementia subtype in this study, we could not investigate this further.

Our study is the first to compare the association between olfaction and dementia in black vs white cognitively normal older adults, despite known differences in OI,[9] dementia risk,[10–13] and related factors, including the prevalence of and cognitive risk associated with both diabetes mellitus[34,35] and *APOE* ε4.[36–38] However, the extent to which these disparities reflect differences in the pathophysiology of AD remains unknown. While differences in olfaction may result from factors unrelated to neurodegenerative processes such as increased exposure to olfactory toxins,[39,40] it is possible that the difference in magnitude of effect between racial groups may result from the high relative prevalence of vascular dementia among blacks[41] or differences in genetic predisposition to dementia.[42–46]

Strengths of this study include the use of a biracial, community-based cohort with a long follow-up period. Few studies have followed up cohorts over a sufficiently long period to study the utility of olfaction for identifying those at risk or even for use as a screen for preclinical neurodegenerative disease, and ours is one of the first with an adequate sample size to detect potentially important interactions and to provide a detailed assessment of potential confounders and comorbidities. While we believe that our comprehensive algorithm represents a relatively conservative approach to classifying incident dementia, we recognize that our definition of dementia has less specificity and sensitivity due to the lack of a full clinical evaluation.

Biomarkers that detect neurodegenerative disease in its presymptomatic stage will be essential to implementing treatment or prevention sufficiently early in

Table 2 Risk of dementia associated with odor identification performance

		Unadjusted		Adjusted for demographics		Fully adjusted	
Olfaction	Dementia, n (%)	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
White							
Poor	114 (33.8)	3.83 (2.85-5.14)	<0.0001	3.45 (2.57-4.65)	<0.0001	3.34 (2.45-4.54)	<0.0001
Moderate	91 (20.0)	2.09 (1.53-2.84)	<0.0001	1.96 (1.43-2.67)	<0.0001	1.84 (1.33-2.54)	0.0002
Good	73 (10.2)	1	—	1	—	1	—
Black							
Poor	84 (31.9)	2.22 (1.62-3.03)	<0.0001	2.00 (1.46-2.75)	<0.0001	2.03 (1.44-2.84)	<0.0001
Moderate	54 (23.3)	1.48 (1.04-2.10)	0.03	1.45 (1.01-2.08)	0.046	1.42 (0.97-2.10)	0.07
Good	75 (17.7)	1	—	1	—	1	—

Abbreviations: CI = confidence interval; HR = hazard ratio.
Fully adjusted for demographics and *APOE* ε4, depression, smoking, physical activity, and body mass index.

the disease course. Unlike the majority of current biomarkers, olfactory testing represents a candidate for widespread utility, having been proven to be a simple, inexpensive, and highly sensitive method of predicting AD development in older adults. This study further validates the use of OI performance as a marker of preclinical dementia among both black and white older adults.

AUTHOR CONTRIBUTIONS

Study concept and design: Yaffe. Drafting/revising manuscript: Yaffe, Freimer, Chen, Asao, Rosso, Rubin, Tranah, Cummings, Simonsick. Interpretation of data: Yaffe, Freimer, Chen, Asao, Rosso, Rubin, Tranah, Cummings, Simonsick. Statistical analysis: Yaffe. Study supervision: Yaffe, Simonsick, Cummings.

STUDY FUNDING

This research was supported by National Institute on Aging contracts N01-AG-6-2101, N01-AG-6-2103, N01-AG-6-2106, R01-AG028050, and K24-AG031155; and National Institute of Nursing Research grant R01-NR012459. The study was supported in part by the Intramural Research Program of the NIH, the National Institute of Environmental Health Sciences (Z01-ES101986).

DISCLOSURE

K. Yaffe and D. Freimer report no disclosures relevant to the manuscript. H. Chen receives NIH intramural funding (Z01-ES-101986) and serves on the editorial boards of the *American Journal of Epidemiology*, *International Journal of Molecular Epidemiology and Genetics*, and *American Journal of Neurodegenerative Disease*. K. Asao became an employee of Eli Lilly Japan, K.K. as of March 1, 2016. The work presented in this manuscript was conducted while Dr. Asao was employed at the University of Tennessee Health Science Center. Eli Lilly Japan, K.K. has no role in this work. A. Rosso, S. Rubin, G. Tranah, S. Cummings, and E. Simonsick report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received April 7, 2016. Accepted in final form October 31, 2016.

REFERENCES

1. Devanand DP, Liu X, Tabert MH, et al. Combining early markers strongly predicts conversion from mild cognitive impairment to Alzheimer's disease. Biol Psychiatry 2008;64:871–879.
2. Wesson DW, Wilson DA, Nixon RA. Should olfactory dysfunction be used as a biomarker of Alzheimer's disease? Expert Rev Neurother 2010;10:633–635.
3. Schofield PW, Finnie S, Yong YM. The role of olfactory challenge tests in incipient dementia and clinical trial design. Curr Neurol Neurosci Rep 2014;14:479.
4. Velayudhan L, Pritchard M, Powell JF, Proitsi P, Lovestone S. Smell identification function as a severity and progression marker in Alzheimer's disease. Int Psychogeriatr 2013;25:1157–1166.
5. Djordjevic J, Jones-Gotman M, De Sousa K, Chertkow H. Olfaction in patients with mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 2008;29:693–706.
6. Devanand DP, Lee S, Manly J, et al. Olfactory deficits predict cognitive decline and Alzheimer dementia in an urban community. Neurology 2015;84:182–189.
7. Stanciu I, Larsson M, Nordin S, Adolfsson R, Nilsson LG, Olofsson JK. Olfactory impairment and subjective olfactory complaints independently predict conversion to dementia: a longitudinal, population-based study. J Int Neuropsychol Soc 2014;20:209–217.
8. Roberts RO, Christianson TJ, Kremers WK, et al. Association between olfactory dysfunction and amnestic mild cognitive impairment and Alzheimer disease dementia. JAMA Neurol 2016;73:93–101.
9. 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.
10. Green RC, Cupples LA, Go R, et al. Risk of dementia among white and African American relatives of patients with Alzheimer disease. JAMA 2002;287:329–336.
11. Tang MX, Cross P, Andrews H, et al. Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. Neurology 2001;56:49–56.
12. Tang MX, Stern Y, Marder K, et al. The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics. JAMA 1998;279:751–755.
13. Alzheimer's Association. 2010 Alzheimer's disease facts and figures. Alzheimers Dement 2010;6:158–194.
14. Harris TB, Visser M, Everhart J, et al. Waist circumference and sagittal diameter reflect total body fat better than visceral fat in older men and women: the Health, Aging and Body Composition Study. Ann N Y Acad Sci 2000;904:462–473.
15. Doty RL, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell identification test (CC-SIT). Laryngoscope 1996;106:353–356.
16. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 1987;48:314–318.
17. Holsinger T, Plassman BL, Stechuchak KM, Burke JR, Coffman CJ, Williams JW Jr. Screening for cognitive impairment: comparing the performance of four instruments in primary care. J Am Geriatr Soc 2012;60:1027–1036.
18. Hong CH, Falvey C, Harris TB, et al. Anemia and risk of dementia in older adults: findings from the Health ABC study. Neurology 2013;81:528–533.
19. Davis TC, Long SW, Jackson RH, et al. Rapid estimate of adult literacy in medicine: a shortened screening instrument. Fam Med 1993;25:391–395.
20. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med 1994;10:77–84.
21. Doty RL, Kamath V. The influences of age on olfaction: a review. Front Psychol 2014;5:20.
22. Vasavada MM, Wang J, Eslinger PJ, et al. Olfactory cortex degeneration in Alzheimer's disease and mild cognitive impairment. J Alzheimers Dis 2015;45:947–958.
23. Wilson RS, Schneider JA, Arnold SE, Tang Y, Boyle PA, Bennett DA. Olfactory identification and incidence of mild cognitive impairment in older age. Arch Gen Psychiatry 2007;64:802–808.
24. Christen-Zaech S, Kraftsik R, Pillevuit O, et al. Early olfactory involvement in Alzheimer's disease. Can J Neurol Sci 2003;30:20–25.
25. Attems J, Walker L, Jellinger KA. Olfactory bulb involvement in neurodegenerative diseases. Acta Neuropathol 2014;127:459–475.
26. Serby M, Larson P, Kalkstein D. The nature and course of olfactory deficits in Alzheimer's disease. Am J Psychiatry 1991;148:357–360.

27. Arnold SE, Lee EB, Moberg PJ, et al. Olfactory epithelium amyloid-beta and paired helical filament-tau pathology in Alzheimer disease. Ann Neurol 2010;67:462–469.
28. Killiany RJ, Hyman BT, Gomez-Isla T, et al. MRI measures of entorhinal cortex vs hippocampus in preclinical AD. Neurology 2002;58:1188–1196.
29. Conti MZ, Vicini-Chilovi B, Riva M, et al. Odor identification deficit predicts clinical conversion from mild cognitive impairment to dementia due to Alzheimer's disease. Arch Clin Neuropsychol 2013;28:391–399.
30. Kovacs T. Mechanisms of olfactory dysfunction in aging and neurodegenerative disorders. Ageing Res Rev 2004;3: 215–232.
31. Duff K, McCaffrey RJ, Solomon GS. The Pocket Smell Test: successfully discriminating probable Alzheimer's dementia from vascular dementia and major depression. J Neuropsychiatry Clin Neurosci 2002;14:197–201.
32. Motomura N, Tomota Y. Olfactory dysfunction in dementia of Alzheimer's type and vascular dementia. Psychogeriatrics 2006;6:19–20.
33. Alves J, Petrosyan A, Magalhaes R. Olfactory dysfunction in dementia. World J Clin Cases 2014;2:661–667.
34. Mayeda ER, Karter AJ, Huang ES, Moffet HH, Haan MN, Whitmer RA. Racial/ethnic differences in dementia risk among older type 2 diabetic patients: the Diabetes and Aging Study. Diabetes Care 2014;37:1009–1015.
35. Rosenstock S, Whitman S, West JF, Balkin M. Racial disparities in diabetes mortality in the 50 most populous US cities. J Urban Health 2014;91:873–885.
36. Hallman DM, Boerwinkle E, Saha N, et al. The apolipoprotein E polymorphism: a comparison of allele frequencies and effects in nine populations. Am J Hum Genet 1991;49:338–349.
37. Corbo RM, Scacchi R. Apolipoprotein E (APOE) allele distribution in the world: is APOE*4 a "thrifty" allele? Ann Hum Genet 1999;63:301–310.
38. Borenstein AR, Mortimer JA, Wu Y, et al. Apolipoprotein E and cognition in community-based samples of African Americans and Caucasians. Ethn Dis 2006;16:9–15.
39. Mohai P, Lantz PM, Morenoff J, House JS, Mero RP. Racial and socioeconomic disparities in residential proximity to polluting industrial facilities: evidence from the Americans' Changing Lives Study. Am J Public Health 2009;99(suppl):S649–S656.
40. Calderon-Garciduenas L, Franco-Lira M, Henriquez-Roldan C, et al. Urban air pollution: influences on olfactory function and pathology in exposed children and young adults. Exp Toxicol Pathol 2010;62:91–102.
41. Froehlich TE, Bogardus ST Jr, Inouye SK. Dementia and race: are there differences between African Americans and Caucasians? J Am Geriatr Soc 2001; 49:477–484.
42. Marden JR, Walter S, Tchetgen Tchetgen EJ, Kawachi I, Glymour MM. Validation of a polygenic risk score for dementia in black and white individuals. Brain Behav 2014;4:687–697.
43. Gottesman RF, Fornage M, Knopman DS, Mosley TH. Brain aging in African-Americans: the Atherosclerosis risk in Communities (ARIC) experience. Curr Alzheimer Res 2015;12:607–613.
44. Evans DA, Bennett DA, Wilson RS, et al. Incidence of Alzheimer disease in a biracial urban community: relation to apolipoprotein E allele status. Arch Neurol 2003;60: 185–189.
45. Murrell JR, Price B, Lane KA, et al. Association of apolipoprotein E genotype and Alzheimer disease in African Americans. Arch Neurol 2006;63:431–434.
46. Desai PP, Hendrie HC, Evans RM, Murrell JR, DeKosky ST, Kamboh MI. Genetic variation in apolipoprotein D affects the risk of Alzheimer disease in African-Americans. Am J Med Genet B Neuropsychiatr Genet 2003;116B: 98–101.