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]

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
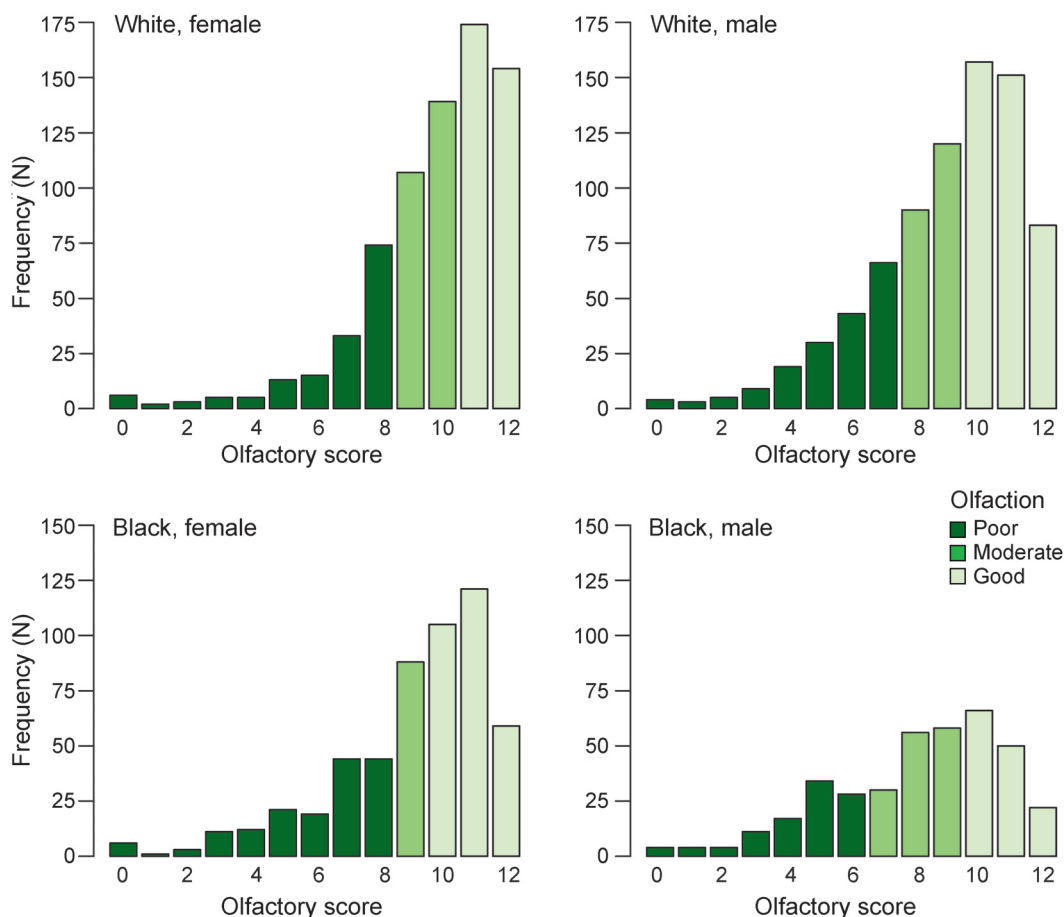
The Kaplan-Meier plot in figure 2 shows differences in dementia incidence by OI group over 12 years of follow-up in both races. Among whites, 33.8% of participants with poor OI developed dementia compared with 10.2% of those with good OI, with an unadjusted hazard ratio (HR) of 3.83 (95% confidence interval [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

Characteristic	White			
	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/m²	25.9 (4.3)	26.4 (4.3)	26.8 (4.0)	<0.01
Characteristic	Black			
	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/m²	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
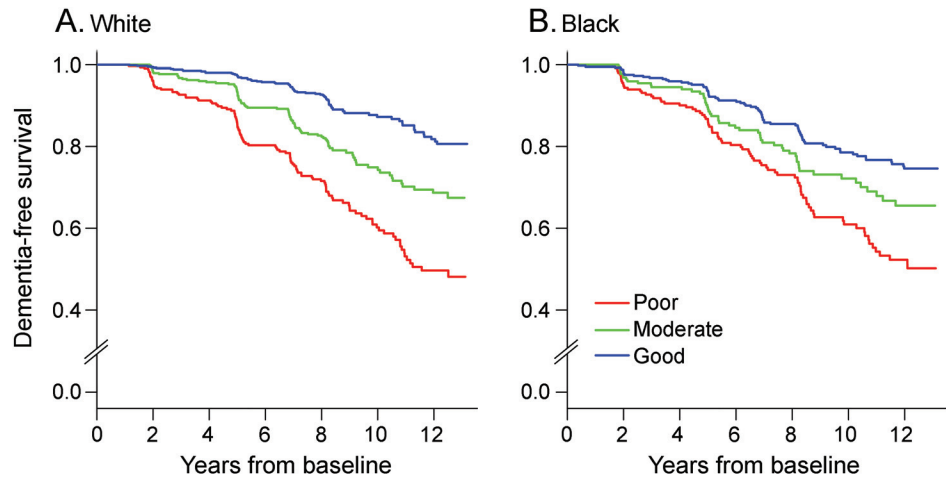
olfactory structures sustained vascular damage, in contrast to the multiple-level impairment observed across the olfactory system in AD pathology.[25,27,30] Because we did not have detailed information on dementia subtype in this study, we could not investigate this further.

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

Olfaction	Dementia, n (%)	Unadjusted		Adjusted for demographics		Fully adjusted	
		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.

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