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Research Article

Olfactory Dysfunction and Depression Trajectories in Community-Dwelling Older Adults

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Abstract

Background: We examined the relationship between baseline olfactory performance and incident significant depressive symptoms and longitudinal depression trajectories in well-functioning older adults. Inflammation and cognitive status were examined as potential mediators.

Methods: Older adults (n = 2 125, 71–82 years, 51% female, 37% Black) completed an odor identification task at Year 3 (our study baseline) of the Health, Aging, and Body Composition study. Cognitive assessments, depressive symptoms, and inflammatory markers were ascertained across multiple visits over 8 years. Discrete-time complementary log-log models, group-based trajectory models, and multivariable-adjusted multinomial logistic regression were employed to assess the relationship between baseline olfaction and incident depression and longitudinal depression trajectories. Mediation analysis assessed the influence of cognitive status on these relationships.

Results: Individuals with lower olfaction had an increased risk of developing significant depressive symptoms at follow-up (hazard ratio = 1.04, 95% confidence interval [CI]: 1.00, 1.08). Of the 3 patterns of longitudinal depression scores identified (stable low, stable moderate, and stable high), poorer olfaction was associated with a 6% higher risk of membership in the stable moderate (relative risk ratio [RRR] = 1.06, 95% CI: 1.02, 1.10)/stable high (RRR = 1.06, 95% CI: 1.00, 1.12) groups, compared to the stable low group. Poor cognitive status, but not inflammation, partially mediated the relationship between olfactory performance and incident depression symptom severity.

Conclusions: Suboptimal olfaction could serve as a prognostic indicator of vulnerability for the development of late-life depression. These findings underscore the need for a greater understanding of olfaction in late-life depression and the demographic, cognitive, and biological factors that influence these relationships over time.

Keywords: Alzheimer's disease, Affective, Dementia, Mood, Olfaction, Smell

Safety concerns, quality of life, inadequate nutritional intake, and reduced pleasure associated with eating all contribute to the scientific and clinical significance of olfactory dysfunction. Olfactory abilities decline with age, and accelerated olfactory loss is observed in persons with Alzheimer's disease (AD) and other neurodegenerative conditions (1). In cognitively unimpaired older adults, olfactory impairment at baseline is independently associated with cognitive decline at follow-up and may aid in the identification of older adults at risk for dementia (2). The shared neurocircuitry between the olfactory system and orbitofrontal–limbic regions has also made smell an informative sensory tool for understanding psychiatric conditions, including major depression and bipolar disorder (3,4). Olfactory impairment can worsen with increasing

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depression severity (5), and individuals experiencing symptom remission through psychotherapy or pharmacotherapy show improved olfactory function (6,7). Most studies of olfactory dysfunction and depression have focused on early and middle adulthood, and comparatively less is known about the relationship between olfaction and depression in late life.

Prior epidemiologic studies of older adults indicate concurrent associations between poor odor identification and higher depressive symptoms, assessed using the Center for Epidemiologic Studies—Depression Scale (8–11). In 1 375 older adults from the Blue Mountains Eye Study, individuals with olfactory impairment had a higher prevalence of depression symptoms. Eliyan et al. (10) examined the relationship between olfaction and depression in a nationally representative sample of older U.S. adults in the National Social Life, Health, and Aging Project (NSHAP) over 15 years. Baseline odor identification impairment in healthy older adults predicted the development of more frequent depressive symptoms 5 and 10 years later. Notably, baseline depression status did not predict incident olfactory dysfunction. These latter findings suggest that olfactory dysfunction may be a prognostic indicator of vulnerability to depression in late life, but few longitudinal studies have tested this hypothesis.

An emerging literature indicates shared mechanisms between late-life depression (LLD) and AD, including reduced hippocampal volume, cerebrovascular disease, and inflammatory processes (12). Cognitive impairment and inflammation have been put forth as potential mediators of the relationship between olfaction disturbance and depression (13,14). Olfactory impairment is more severe in older adults with major depression and comorbid cognitive impairment (15). Chen et al. (16) found that persons with both LLD and olfactory loss had more severe cognitive impairment across measures of memory, language, executive functioning, and attention, as well as reduced gray matter volumes in AD-related brain regions of interest, than those with LLD without impaired olfaction. Several inflammatory markers, including interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), interleukin-1-beta (IL-1β), and glucocorticoids, are elevated in persons with LLD (17). These elevations may be associated with hippocampal neurogenesis and olfactory neuron proliferation. Human studies have shown associations between olfactory performance and inflammation. In particular, elevated blood plasma levels of IL-6 have been reported in individuals with olfactory loss (18,19), and C-reactive protein (CRP) elevations were found to be associated with olfactory impairment in a dose–response fashion in a large Swedish study of aging (20).

Though olfactory loss and depression have been examined as independent predictors of incipient dementia, the relationship between baseline olfactory dysfunction and depression trajectories and the potential influence of cognitive dysfunction and inflammation have yet to be examined. In the current study, we examined the relationship between baseline odor identification performance and (a) incident clinically significant depressive symptoms; and (b) depression trajectories over an 8-year follow-up period. We also examined whether inflammation and cognitive functioning influence the longitudinal relationship between olfaction and depression. Based on prior work (10), we hypothesized that baseline olfactory dysfunction is associated with (a) an increased risk of developing or having significant depressive symptoms and (b) membership in the consistently moderate to high depression trajectory. We anticipated that olfactory impairment would be associated with greater cognitive dysfunction and elevated inflammatory markers, particularly IL-6 and CRP.

Method

Study Population

The Health, Aging, and Body Composition (Health ABC) study is a prospective cohort study with 3 075 Black and White well-functioning older adults aged 70–79 years (52% female, 42% Black) at baseline (1997–1998) from a random sample of Medicare beneficiaries in Memphis, Tennessee, and Pittsburgh, PA (21). Eligible participants had no self-reported difficulties in walking 1/4 mile, climbing 10 steps or performing activities of daily living, no known life-threatening cancers, and no plan to move out of the area within 3 years (21). Participants attended clinic examinations annually and were contacted semiannually by telephone. Written informed consent was obtained from all participants and the study was approved by the institutional review boards at both sites. The first and only assessment of olfaction occurred at Year 3 (1999–2000). Thus, Year 3 served as our baseline for analysis. A total of 2 967 Health ABC participants were alive at Year 3. We excluded 49 participants with prevalent dementia, 415 participants with missing olfactory testing, and 23 participants with missing covariates, leaving 2 480 participants. From the main analyses of the association of olfactory impairment and incident depression, 355 participants who had prevalent depression at Year 3 were also excluded, resulting in 2 125 participants. However, these 355 participants were included in secondary analyses of olfaction and trajectories of depressive symptoms over time.

Of the 2 967 Health ABC participants alive at Year 3, the 2 125 participants included in our main analyses were younger, less likely to self-identify as female or Black, more likely to come from the Pittsburgh site and have postsecondary education. Participants in the analytical sample were also more likely to currently drink alcohol, had higher levels of physical activity, and were less likely to have cardiovascular conditions (Supplementary Table 1).

Depressive Symptoms

Depressive symptoms were measured using the 10-item Center for Epidemiologic Studies—Depression Scale (CES-D-10) at Years 3, 4, 5, 6, 8, 10, and 11, where participants reported the frequencies of their feelings and behaviors in the past week (22). Total score ranges from 0 to 30 and a higher score indicates the presence of more depressive symptomatology. At Years 3, 5, and 6, participants also reported their use of antidepressants. Having clinically significant depressive symptoms was defined as a CES-D-10 score ≥10 and/or self-reported use of antidepressants (Years 3, 5, and 6 only) based on prior work (22). For analysis, the CES-D-10 score was also considered continuously.

Olfaction

Olfaction was measured at Year 3 (1999–2000) using the Brief Smell Identification Test (B-SIT), a 12-item screening test for odor identification impairment (23,24). During the test, participants were presented with 12 common odorants and asked to identify the odorant from 4 options. Each

correct answer was assigned 1 point and the total score was summed, ranging from 0 to 12. The B-SIT score was analyzed continuously and categorically (normosmia, hyposmia, or anosmia) using established cut points based on race- and sex-stratified tertiles (normosmia [White women: 11–12, White men: 10–12, Black women: 10–12, Black men: 10–12]; Hyposmia [White women: 9–10, White men: 8–9, Black women: 9, Black men: 7–9]; anosmia [White women: <9, White men: <8, Black women: <9, Black men: <7]) (2).

Cognitive Performance

Cognitive status was assessed with the Modified Mini-Mental State Exam (3MS; 25) and the Digit Symbol Substitution Test (DSST; 26) at Years 1, 3, 5, 8, 10, and 11. The 3MS is adapted from the 30-item Mini-Mental State Exam (MMSE; 27) and assesses temporal and spatial orientation, mental reversal, naming, conceptual similarities, repetition, word recall, language comprehension, writing, and visuoconstruction with a score range of 0–100. The DSST is a measure of visual scanning, attention, and speeded processing. Participants are shown a key of 9 number–symbol pairs. A series of numbers without the corresponding symbols are presented, and participants are asked to fill in the corresponding symbol as quickly as possible using the key. The number of correct symbols completed within 90 seconds is summed. For analysis, 3MS and DSST scores were standardized to *Z*-scores with a mean of 0 and standard deviation of 1 to facilitate comparison.

Inflammatory Measures

Methods for ascertaining and measuring serum or plasma concentrations of CRP, IL-6, and TNF-α are described in detail in prior work (28). Briefly, fasted blood samples were acquired through venipuncture and concentrations of each marker were ascertained from stored frozen samples in duplicate using R&D Systems ELISA kits (Minneapolis, MN). For IL-6, the detectable limit using the HS600 Quantikine kit was 0.10 pg/mL. For TNF-α, the detectable limit using the HSTA50 kit was 0.18 pg/mL. For CRP, the assay was standardized using the World Health Organization First International Reference Standard with a sensitivity of 0.08 mg/L and a lower detection limit of 0.007 mg/L. Blind duplicate analyses were conducted in a subset of samples (n = 150) for CRP, IL-6, and TNF-α and demonstrated an inter-assay coefficients of variation of 8.0%, 10.3%, and 15.8%, respectively (28).

Other Covariates

Demographic information was collected at Year 1 (1997–1998), including age (years), natal sex (male; female), race (White; Black), education (less than high school; high school graduate; postsecondary), and study site (Memphis; Pittsburgh). Smoking status (never, former, or current smoker) and body mass index (BMI) in kg/m^2 calculated from measured height and weight were collected at Year 3 (1999–2000). Alcohol use status (never, former, or current drinker) was self-reported at Year 1. Number of minutes spent walking briskly served as a surrogate measure of physical activity and was analyzed categorically depending on whether participants walked briskly for at least 90 minutes per week. Apolipoprotein E (*APOE*) genotypes were obtained using single nucleotide polymorphism genotyping techniques (Bioserve, Ltd., Laurel, MD) and were categorized as having ≥1 or no *APOE* ε4 allele.

Hypertension, diabetes, and stroke were defined according to prespecified algorithms in Health ABC. Briefly, the presence of diabetes was defined as self-report of physician-diagnosed diabetes, use of diabetes medications, or a fasting glucose ≥126 mg/dL. The presence of hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure >90 mmHg, or by self-report of physician-diagnosed hypertension with or without the use of antihypertensive medications. The presence of stroke was self-reported and hospital records were collected and verified. Other comorbidities, including coronary heart disease, myocardial infarction, cancer, chronic lung disease, ulcer, peripheral arterial disease, osteoarthritis, and musculoskeletal/connective tissue disorder, were also defined according to prespecified algorithms in Health ABC.

Statistical Analysis

Descriptive Analysis

Participant characteristics were compared using analysis of variance (ANOVA) for continuous variables and Pearson chi-squared tests for categorical variables.

Olfactory Dysfunction and Incident Depression

Olfaction and time to first incidence of clinically significant depressive symptoms were modeled using a discrete-time complementary log-log model. The first and only assessment occurred at Year 3. As such, Year 3 served as the time origin and participants were followed until Year 11 (2007–2008). Models were adjusted for age, sex, race, education, study site, smoking, alcohol use, BMI, physical activity, hypertension, diabetes, and stroke.

Given the associations of olfactory impairment with mortality and dementia (2,29–31), participants with olfactory impairment might be more likely to drop out, preventing follow-up assessment of depressive symptoms. To aid in our interpretation of the cause-specific association between olfactory impairment and depressive symptoms, we conducted competing risk analyses using Cox proportional hazards models to estimate (a) cause-specific hazard of death without depression associated with olfactory impairment with depression events before death censored and (b) cause-specific hazard of dementia without depression associated with olfactory impairment with depression events before dementia diagnoses censored.

Cognitive performance and inflammation are 2 proposed potential mediators of the association between olfaction and depression. We first examined cross-temporal and longitudinal associations of olfaction with cognitive performance and inflammatory markers (TNF-α, IL-6, and CRP), respectively. We observed associations between olfactory impairment at Year 3 and worse performance on 3MS and DSST at Year 5 (Supplementary Table 2) as well as a faster decline in 3MS and DSST over follow-up (Supplementary Table 3). Therefore, we conducted a mediation analysis of the olfaction–depression association to quantify the contribution of interaction and mediating mechanisms through cognitive performance (32). The overall olfaction–depression association was decomposed into direct effect (the sum of controlled direct effect [due to neither mediation nor interaction] and reference interaction [due to interaction only]) and indirect effect (the sum of pure indirect effect [due to mediation only] and mediated interaction [due to both mediation

and interaction]). In contrast, we did not find associations between olfactory impairment and worse inflammatory markers (Supplementary Table 4) and changes in inflammatory markers over follow-up (Supplementary Table 5), and so did not conduct mediation analyses with the inflammatory markers.

Prior studies have demonstrated an accelerated olfactory decline in *APOE* ε4 allele carriers and shown differences in the relationship between olfaction and depression by health status (eg, presence or absence of medical comorbidities) (10,33). As such, we conducted secondary analyses to explore whether the association between olfaction and depression differed by *APOE* ε4 (≥1 vs 0 allele) and the number of comorbidities (≥1 vs 0 comorbidity).

Olfactory Dysfunction and 8-Year Depression Trajectories

With continuous CES-D-10 scores assessed over 8 years of follow-up, participants followed their individual trajectories. To summarize the individual trajectories in a parsimonious and interpretable way, we used group-based trajectory models to identify groups of participants with similar patterns of CES-D-10 score trajectories over follow-up (34). This method is not based on a priori classification of the trajectories. Instead, participants were assigned to trajectory groups based on the estimated probabilities of group membership. The performance of the models was assessed using the Akaike information criterion, the Bayesian information criterion, and entropy. The number of participants in each trajectory group was also considered. Three trajectory groups were identified: (a) stable low CES-D-10 score; (b) stable moderate CES-D-10 score; and (c) stable high CES-D-10 score (Supplementary Figure 1: trajectory groups).

Multivariable-adjusted multinomial logistic regression was then used with latent class membership as the outcome to estimate the relative risk ratio (RRR) of depressive symptom trajectories by olfaction status. Models were similarly adjusted for age, sex, race, education, study site, smoking, alcohol use, BMI, physical activity, hypertension, diabetes, and stroke. Sensitivity analyses considering antidepressant medication use were also conducted.

All analyses were conducted using Stata version 17.0 (Stata Corporation, College Station, TX) and a 2-sided p value of <.05 was considered statistically significant.

Results

Descriptive Analysis

Among 2 125 participants, 1 019 (48%) had normosmia, 587 (28%) had hyposmia, and 519 (24%) had anosmia. Participants with better olfaction were younger, less likely to self-identify as Black, more likely to be enrolled at the Pittsburgh site, and more likely to have higher educational attainment, never smoking, current alcohol use, and higher BMI (Table 1). Of note, 522 (25%) participants developed clinically significant depressive symptoms over follow-up (mean: 6 years, range: 0–9 years). Compared to the remaining 1 603 participants, participants who developed clinically significant depressive symptoms had lower education attainment and were more likely to be female, have never smoked, have lower levels of physical activity, have a higher prevalence of hypertension and diabetes, and drink less alcohol at baseline (Supplementary Table 6).

Olfactory Dysfunction and Incident Depressive Symptoms

When modeled continuously, every 1-point lower (worse) B-SIT score was associated with a significantly increased risk of significant depressive symptoms (hazard ratio [HR] = 1.04, 95% confidence interval [CI]: 1.00, 1.08), even after full adjustment. When modeled categorically, after full adjustment, compared to normosmia, neither hyposmia (HR = 1.13, 95% CI: 0.92, 1.40) nor anosmia (HR = 1.22, 95% CI: 0.98, 1.51) was statistically significantly associated with an increased risk of significant depressive symptoms over time, although the estimate for hyposmia was borderline (p = .07; Figure 1 and Supplementary Table 7, Model 3).

In competing risk analysis, we found significant associations between lower (worse) olfactory score and higher risk of mortality without depression (HR = 1.05, 95% CI: 1.01, 1.09) and dementia without depression (HR = 1.49, 95% CI: 1.27, 1.75; Table 2). Olfactory performance groups showed overall consistent results: When compared to normosmia, hyposmia was associated with a higher risk of dementia without depression (HR = 1.76, 95% CI: 1.27, 2.44) but not death; anosmia was associated with both mortality without depression (HR = 1.28, 95% CI: 1.02, 1.62) and dementia without depression (HR = 2.24, 95% CI: 1.62, 3.09; Table 2).

In a mediation analysis considering global cognitive status, we found minimal contributions from interaction mechanisms (reference interaction and mediated interaction). Therefore, the direct effect consists of the controlled direct effect due to neither mediation nor interaction only, contributing to 60% of the overall olfaction–depression association. The indirect effect consists of the pure indirect effect due to mediation through cognitive status only, contributing to 40% of the overall association (Table 3). In summary, olfactory impairment affects depressive symptoms directly (60%) and also affects through cognition (40%).

Although the p value for interaction between olfaction and *APOE* e4 carrier status was not statistically significant, we estimated qualitative differences in the association between olfactory dysfunction and incident depression, with estimates suggesting increased risk among those with no e4 alleles and null associations among those with ≥1 e4 allele. This was particularly pronounced for anosmia (vs normosmia), in which the association was 1.39 (95% CI: 1.08, 1.80) among those with no e4 alleles, but 0.95 (0.63, 1.43) among e4 carriers (Supplementary Table 8). Similarly, estimates for the olfaction–depression association among participants with no comorbidities were null, but suggested increased risk among participants with at least one comorbidity. Compared to normosmia, participants with anosmia had an HR of 1.01 (95% CI: 0.64, 1.59) and 1.28 (95% CI: 1.01, 1.63) when restricted to participants with 0 versus ≥1 comorbidities, respectively (Supplementary Table 9). The p value for interaction did not reach statistical significance, however (p = 0.36).

Olfactory Dysfunction and 8-Year Depression Trajectories

Participants were classified into 3 depressive symptoms trajectories over time: 1 189 (48%) participants had stable low CES-D-10 scores over time, 1 018 (41%) had stable moderate CES-D-10 scores over time, and 273 (11%) had stable high CES-D-10 scores. Every 1-point lower (worse) in B-SIT score was associated with a higher risk of being in the stable moderate (RRR = 1.06, 95% CI: 1.02, 1.10) and stable high

Table 1. Baseline (Year 3, 1999–2000) Demographic and Clinical Characteristics of Study Cohort by Olfaction Status, the Health Aging and Body Composition Study, *N* = 2 125

	Total Cohort, *N* = 2 125	Olfaction*			*p* Value†
		Normosmia, *N* = 1 019	Hyposmia, *N* = 587	Anosmia, *N* = 519	
Age (year), mean (*SD*)	75.5 (2.8)	75.2 (2.7)	75.7 (3.0)	76.0 (2.9)	<.001
Female, *N* (%)	1 073 (50.5)	522 (51.2)	280 (47.7)	271 (52.2)	.26
Black, *N* (%)	789 (37.1)	373 (36.6)	194 (33.0)	222 (42.8)	.003
Education, *N* (%)					<.001
Less than high school	442 (20.8)	171 (16.8)	131 (22.3)	140 (27.0)	
High school graduate	690 (32.5)	326 (32.0)	203 (34.6)	161 (31.0)	
Postsecondary	993 (46.7)	522 (51.2)	253 (43.1)	218 (42.0)	
Pittsburgh site, *N* (%)	1 089 (51.2)	557 (54.7)	276 (47.0)	256 (49.3)	.01
Smoking, *N* (%)					.01
Never	963 (45.3)	472 (46.3)	254 (43.3)	237 (45.7)	
Current	154 (7.2)	57 (5.6)	42 (7.2)	55 (10.6)	
Former	1 008 (47.4)	490 (48.1)	291 (49.6)	227 (43.7)	
Alcohol use‡, *N* (%)					<.001
Never	588 (27.7)	288 (28.3)	147 (25.0)	153 (29.5)	
Current	1 094 (51.5)	556 (54.6)	300 (51.1)	238 (45.9)	
Former	443 (20.8)	175 (17.2)	140 (23.9)	128 (24.7)	
BMI (kg/m^2), mean (*SD*)	27.2 (4.7)	27.6 (4.7)	26.8 (4.5)	26.9 (5.0)	.001
Brisk walking ≥90 min/wk, *N* (%)	233 (11.0)	126 (12.4)	63 (10.7)	44 (8.5)	.07
Hypertension, *N* (%)	1 180 (55.5)	567 (55.6)	335 (57.1)	278 (53.6)	.50
Diabetes, *N* (%)	439 (20.7)	206 (20.2)	118 (20.1)	115 (22.2)	.62
Stroke, *N* (%)	171 (8.0)	79 (7.8)	53 (9.0)	39 (7.5)	.58
CES-D-10 score, mean (*SD*)	3.3 (2.6)	3.1 (2.5)	3.4 (2.6)	3.4 (2.7)	.03

Notes: ANOVA = analysis of variance; BMI = body mass index; CES-D = Center of Epidemiologic Studies—Depression Scale; *N* = sample size; *SD* = standard deviation.
*Olfaction was categorized according to race- and sex-stratified tertiles of the 12-item Brief Smell Identification Test: normosmia (White females: 11–12; White males: 10–12; Black females: 10–12; Black males: 10–12); hyposmia (White females: 9–10; White males: 8–9; Black females: 9; Black males: 7–9); anosmia (White females: <9; White males: <8; Black females: <9; Black males: <7).
†*p* Values were calculated by ANOVA for continuous variables and Pearson chi-squared test for categorical variables.
‡Alcohol use status was collected instead at Year 1 (1997–1998).

(RRR = 1.06, 95% CI: 1.00, 1.12) groups when compared to the stable low group (Table 4). Participants with hyposmia were more likely to have stable moderate CES-D trajectory (RRR = 1.24, 95% CI: 1.01, 1.52) but not stable high CES-D trajectory (RRR = 1.23, 95% CI: 0.89, 1.71) when compared to the stable low CES-D group. Participants with anosmia were more likely to have stable moderate (RRR = 1.33, 95% CI: 1.07, 1.65) and stable high (RRR = 1.40, 95% CI: 1.00, 1.96) CES-D trajectories, compared to membership in the stable low group. In sensitivity analysis, adjusting for antidepressant medication or limiting to 2 063 participants without antidepressant medication use yielded similar estimates (Supplementary Table 10).

Discussion

To our knowledge, the current study is the first to examine the relationship between baseline olfaction and longitudinal depression trajectories in older adults. Previous studies in older adults have found cross-sectional relationships between odor identification ability and self-reported depressive symptoms (8–11), and between baseline olfactory impairment and higher depressive symptoms at 5- and 10-year follow-ups (10). In this prospective longitudinal cohort study of 2 125 community-dwelling older adults, individuals with impaired odor identification were at increased risk of developing a clinically significant level of depressive symptoms at subsequent visits. This relationship was more robust when odor identification score was modeled continuously. Consistent with multiple prior studies (29), poor olfaction was associated with all-cause mortality and incident dementia, which may have diminished or altered the chance of observing incident report of significant depressive symptoms in this sample.

In addition to associations with an increased risk of depression over time, reduced odor identification was associated with depressive symptom trajectories over time. We identified 3 patterns of depression scores over 8 years in this cohort: stable low, stable moderate, and stable high depressive scores. Poorer olfaction was associated with an increased risk of membership in the stable moderate or high groups, compared to the stable low group. These findings persisted after adjustment for demographic, lifestyle/health factors and antidepressant medication use. The severity of odor identification impairment corresponded with membership in the stable moderate or high depression trajectories. Indeed, participants with more marked odor identification impairment at baseline were more likely to be in the consistently moderate to high depression trajectories.

Multiple explanations have been put forth to explain the relationship between loss of smell and depression (4).

Olfaction has an important yet underappreciated role in human health and behavior. Poor smell has been linked to decreased sexual motivation, poor grooming and hygiene, and reduced quality of life, all of which can ultimately affect mood states (35). In older adults, diminished olfaction is associated with increased feelings of loneliness (8) and lower reported social life in women (36), defined as the number of friends, close relatives, and frequency of socializing. Factors such as appetite, feeding behavior, and enjoyment of food can also be influenced by reduced olfaction. In a prior Health ABC study of community-dwelling older adults, poor olfaction at baseline was associated with lower total and fat mass, and higher annual decrease in total and fat mass (37). Taken together, there are multiple behavioral pathways by which poor smell may influence incident depressive symptoms, ranging from poor appetite and anhedonia to weight loss.

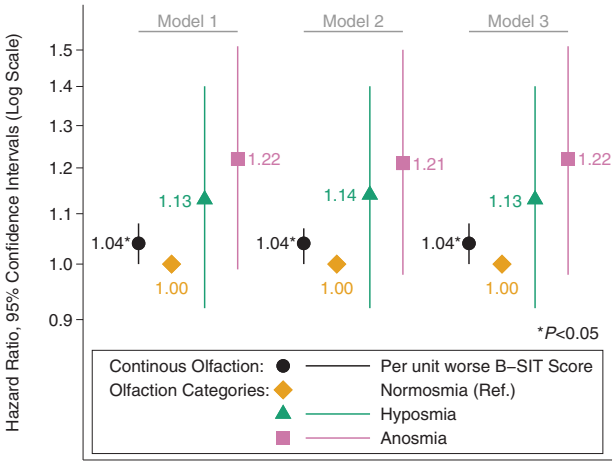

Figure 1. Multivariable-adjusted associations between olfaction and time to first incident occurrence of significant depressive symptoms, the Health Aging and Body Composition Study, *N* = 2 125. Ref = reference; B-SIT = Brief Smell Identification Test. [a]Model 1 adjusted for age, sex, race, education, and study site. [b]Model 2 adjusted for Model 1 + smoking, alcohol use, body mass index, and physical activity. [c]Model 3 adjusted for Model 2 + hypertension, diabetes, and stroke. [d]Olfaction was categorized according to race- and sex-stratified tertiles of the 12-item B-SIT: normosmia (White females: 11–12; White males: 10–12; Black females: 10–12; Black males: 10–12); hyposmia (White females: 9–10; White males: 8–9; Black females: 9; Black males: 7–9); anosmia (White females: <9; White males: <8; Black females: <9; Black males: <7). Olfaction was also modeled continuously as per point lower (worse) 12-item B-SIT score.

Olfactory measures may also serve as robust correlates of persistent depressive symptoms due, in part, to the neuroanatomical integration of olfactory regions with orbitofrontal and limbic neurocircuitry. In individuals with major depression, structural and functional changes in the peripheral olfactory system are observed, ranging from abnormal olfactory event-related potentials and altered olfactory sulcal depth to reduced olfactory bulb (OB) size (38–41). Across 3 studies of depression, smaller OB volumes were associated with higher depression severity (39,40,42). The peripheral olfactory system first projects olfactory information to the OBs, and from there, information is relayed to the amygdala and hippocampus largely independent of the thalamus. It has been posited that peripheral olfactory system abnormalities may diminish input to the amygdala, hippocampus, and other limbic regions, which can alter neurotransmitter turnover and serotonin synthesis. In healthy individuals, olfactory performance is correlated with amygdala, entorhinal, and hippocampal volumes (43,44), brain regions known to be affected in LLD. Furthermore, in animal models of depression, olfactory bulbectomy leads to hippocampal–amygdala dysfunction, resulting in neurophysiological, endocrine, and immunological changes that mirror the major depressive state in humans (45). Taken together, suboptimal olfactory function may serve as a prognostic indicator of vulnerability for the development

Table 2. Competing Risk Analysis of Olfaction and Nondepression Deaths/Dementia, the Health Aging and Body Composition Study, *N* = 2 125

Olfaction[§]	$N_{Outcome}/N_{Total}$	Model 1[*]		Model 2[†]		Model 3[‡]	
		HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Death without depression (*N* = 2 121)							
Per-unit worse B-SIT score		**1.05 (1.01, 1.09)**	**.01**	**1.05 (1.01, 1.09)**	**.02**	**1.05 (1.01, 1.09)**	**.01**
Normosmia	190/1 016	Ref.	—	Ref.	—	Ref.	—
Hyposmia	135/587	1.22 (0.97, 1.52)	.09	1.17 (0.94, 1.47)	.16	1.16 (0.93, 1.46)	.18
Anosmia	127/518	**1.32 (1.05, 1.66)**	**.02**	**1.26 (1.00, 1.59)**	**.05**	**1.28 (1.02, 1.62)**	**.03**
P-trend		**0.01**		**0.04**		**0.03**	
Dementia without depression (*N* = 2 125)							
Per-unit worse B-SIT score		**1.51 (1.29, 1.77)**	**<.001**	**1.48 (1.27, 1.73)**	**<.001**	**1.49 (1.27, 1.75)**	**<.001**
Normosmia	73/1 019	Ref.	—	Ref.	—	Ref.	—
Hyposmia	74/587	**1.81 (1.31, 2.51)**	**<.001**	**1.74 (1.26, 2.41)**	**.001**	**1.76 (1.27, 2.44)**	**.001**
Anosmia	83/519	**2.30 (1.67, 3.17)**	**<.001**	**2.20 (1.60, 3.04)**	**<.001**	**2.24 (1.62, 3.09)**	**<.001**
P-trend		**<0.001**		**<0.001**		**<0.001**	

Notes: B-SIT = Brief Smell Identification Test; CI = confidence interval; HR = hazard ratio; Ref = reference. Bold values indicate statistical significance ($p \leq .05$).
[*]Model 1 adjusted for age, sex, race, education, and study site.
[†]Model 2 adjusted for Model 1 + smoking, alcohol use, body mass index, and physical activity.
[‡]Model 3 adjusted for Model 2 + hypertension, diabetes, and stroke.
[§]Olfaction was categorized according to race- and sex-stratified tertiles of the 12-item Brief Smell Identification Test: normosmia (White females: 11–12; White males: 10–12; Black females: 10–12; Black males: 10–12); hyposmia (White females: 9–10; White males: 8–9; Black females: 9; Black males: –9); anosmia (White females: <9; White males: <8; Black females: <9; Black males: <7). Olfaction was also modelled continuously as per point lower (worse) 12-item B-SIT score.

Table 3. Decomposition of Associations between Olfaction and Time to First Incident Occurrence of Significant Depressive Symptoms* Due to Mediation and Interaction With Cognitive Status, the Health Aging and Body Composition Study, *N* = 2 125

Component	Excess Relative Risk	95% CI	Proportion Attributable (%)
Hyposmia vs normosmia (Ref.)			
Controlled direct effect (CDE)	0.06	−0.07, 0.19	60
Reference interaction (INT_{ref})	0.00	−0.02, 0.02	0.05
Mediated interaction (INT_{med})	−0.00	−0.02, 0.02	−0.65
Pure indirect effect (PIE)	**0.04**	**0.00, 0.07**	40
Total	0.09	−0.04, 0.22	100
Overall proportion attributable to pure direct effect (PDE) = (CDE + INT_{ref})/Total			60
Overall proportion attributable to total indirect effect (TIE) = (PIE + INT_{med})/Total			40
Anosmia vs normosmia (Ref.)			
CDE	0.12	−0.16, 0.39	61
INT_{ref}	0.00	−0.04, 0.04	0.17
INT_{med}	−0.00	−0.09, 0.08	−1.6
PIE	**0.08**	**0.00, 0.15**	41
Total	0.19	−0.09, 0.47	100
Overall proportion attributable to PDE = (CDE + INT_{ref})/Total			61
Overall proportion attributable to TIE = (PIE + INT_{med})/Total			39

Notes: CI = confidence interval; Ref = reference. Bold values indicate statistical significance ($p \leq .05$).
*Model adjusted for age, sex, race, education, study site, smoking, alcohol use, body mass index, physical activity, hypertension, diabetes, and stroke.

Table 4. Multivariable-Adjusted Associations Between Olfaction and Depressive Symptoms Trajectory Groups, the Health Aging and Body Composition Study, *N* = 2 480

Olfaction*	Depressive Symptom Trajectory Groups					
	Stable Low (*N* = 1 189)		Stable Moderate (*N* = 1 018)		Stable High (*N* = 273)	
	RRR (95% CI)	*p* Value	RRR (95% CI)	*p* Value	RRR (95% CI)	*p* Value
Model 1†						
Per-unit worse B-SIT score	Ref.	—	**1.06 (1.02, 1.10)**	**.002**	1.05 (1.00, 1.12)	.06
Normosmia	Ref.	—	Ref.	—	Ref.	—
Hyposmia	Ref.	—	**1.25 (1.02, 1.54)**	**.03**	1.23 (0.88, 1.70)	.22
Anosmia	Ref.	—	**1.35 (1.09, 1.67)**	**.01**	1.38 (0.99, 1.92)	.06
P-trend	Ref.	—	**0.004**		**0.05**	
Model 2‡						
Per-unit worse B-SIT score	Ref.	—	**1.06 (1.02, 1.10)**	**.004**	1.06 (1.00, 1.12)	.06
Normosmia	Ref.	—	Ref.	—	Ref.	—
Hyposmia	Ref.	—	**1.24 (1.01, 1.52)**	**.04**	1.23 (0.88, 1.71)	.22
Anosmia	Ref.	—	**1.32 (1.06, 1.64)**	**.01**	1.38 (0.99, 1.94)	.06
P-trend	Ref.	—	**0.01**		**0.05**	
Model 3§						
Per-unit worse B-SIT score	Ref.	—	**1.06 (1.02, 1.10)**	**.004**	1.06 (1.00, 1.12)	.06
Normosmia	Ref.	—	Ref.	—	Ref.	—
Hyposmia	Ref.	—	**1.24 (1.01, 1.52)**	**.04**	1.23 (0.89, 1.71)	.21
Anosmia	Ref.	—	**1.33 (1.07, 1.65)**	**.01**	**1.40 (1.00, 1.96)**	**.05**
P-trend	Ref.	—	**0.01**		**0.04**	

Notes: B-SIT: Brief Smell Identification Test; CI: confidence interval; Ref: reference; RRR: relative risk ratio. Bold values indicate statistical significance ($p \leq .05$).
*Olfaction was categorized according to race- and sex-stratified tertiles of the 12-item Brief Smell Identification Test: normosmia (White females: 11–12; White males: 10–12; Black females: 10–12; Black males: 10–12); hyposmia (White females: 9–10; White males: 8–9; Black females: 9; Black males: 7–9); anosmia (White females: <9; White males: <8; Black females: <9; Black males: <7). Olfaction was also modelled continuously as per point lower (worse) 12-item B-SIT score.
†Model 1 adjusted for age, sex, race, education, and study site.
‡Model 2 adjusted for Model 1 + smoking, alcohol use, body mass index, and physical activity.
§Model 3 adjusted for Model 2 + hypertension, diabetes, and stroke.

of depression through its projections to the amygdala, hippocampus, and other reward-related brain regions. In particular, poor olfaction may indicate limbic dysfunction that leaves an individual more susceptible to developing LLD.

Given the relevance of olfaction and depression to the preclinical stages of dementia, there has been increasing attention on the relationship between reduced olfactory and cognitive abilities in major depression. In cross-sectional studies of LLD, olfactory impairment has been associated with greater cognitive dysfunction (15,16,46). Liu et al. (13) additionally found that the link between olfaction and cognitive performance may be influenced by the timing of the first depressive episode before (early-onset) or after (late onset) age 60. Though the magnitude of olfactory impairment was greater in late-onset cases, cognitive and olfactory performances were associated in early-onset but not late-onset cases. Moreover, differences in odor identification between early- and late-onset cases were partially mediated by cognitive performance, as assessed with measures of verbal learning and confrontation naming. Our findings expand on prior work by examining the association of cognitive functioning with the longitudinal relationship between olfactory dysfunction and depressive symptoms. In the current study, poor baseline olfactory performance was associated with worsening global cognitive performance (3MS) and worsening visual scanning, attention, and speeded processing (DSST). In addition, analyses stratified by APOE allele status indicated that the relationship between poor olfaction and incident depression may be more robust in persons *without* the e4 allele, which was unexpected. Indeed, large population-based studies of cognitively unimpaired older adults have demonstrated that odor identification is impaired in *APOE*-ε4 allele carriers, and unexplained olfactory dysfunction in the presence of 1 or more APOE-ε4 alleles is associated with a high risk of cognitive decline. These findings suggest potential differences in associations between olfaction and depression in those on versus off the AD trajectory. Our mediation analysis found contributions of cognition to the relationship between olfaction and depressive symptom severity. However, this accounted for ~40% of the estimated effect, with an estimated 60% of the association independent of changes in cognition. Taken together, these findings suggest that the relationship between odor identification and clinically significant depressive symptoms in late life is partially, but not completely, explained by cognitive functioning. That we estimated stronger associations between olfactory dysfunction and depression among participants without a genetic risk for AD also supports our findings of an independent effect of olfaction on depression. Studies with more detailed assessment of cognition and mood will be helpful to clarify this relationship further.

Prior work by Eliyan et al. (10) from the NSHAP found that the longitudinal relationship between baseline olfaction and development of persistent depressive symptoms was influenced by the presence of comorbid medical conditions. In particular, baseline olfactory dysfunction was significantly associated with subsequent depression in individuals without comorbidities but this relationship was not statistically significant in those with medical comorbidities. Given these prior findings, we sought to examine this relationship in the current study. The overall interaction was not statistically significant; however, contrary to prior work (10), we did observe stronger associations between olfactory dysfunction and incident depression in those with other comorbidities. This may reflect the observation that anosmia in older adulthood has been repeatedly linked to poor health status, increased mortality risk, and frailty status, particularly when frailty is defined using an index of medical comorbidities (29,47). All of these factors are also associated with an increased risk of depression. Future studies are needed to increase our understanding of the relationships between olfactory impairment, depression, and health status.

The strengths of this study include the large cohort of Black and White older adults with comprehensive longitudinal follow-up. We were also able to investigate the potential mediation of the olfaction–depression association by cognitive status and inflammation. There were several limitations to this work. Similar to prior studies, depression assessment was limited to the use of symptom screening instrument. Future studies characterizing depression with a structured clinical interview would be helpful. Factors such as chronic rhinosinusitis and pack-years were not assessed. Given the potential link between rhinosinusitis and depression, this variable will be important to consider in future studies (48,49). Smoking was assessed as a categorical variable in our analyses as pack-years was only collected at Year 1 of the Health ABC study. Furthermore, our categorization of olfactory impairment was based on sex- and race-stratified tertiles consistent with a previous Health ABC study; therefore, we were not able to test if the olfactory dysfunction–depression association in our study differed by sex or race. Olfactory function was limited to a single domain and prior studies of depression indicate that patient-control differences may vary as a function of task type. The inclusion of odor detection threshold, for example, would strengthen our understanding of the relationship between olfaction and depression. Prior work has demonstrated that measures of odor identification demonstrate stronger associations with cognitive measures compared to odor detection threshold (50). Inclusion of a less cognitively mediated olfactory test in future studies could further elucidate the influence of cognition on the olfactory–depression relationship. Patients reporting chemosensory distortions report higher levels of depression. Thus, expanding the assessment of olfaction to include self-reported parosmias may be useful to assess in LLD. Finally, the cognitive assessment was limited to the 3MS and DSST. Future studies with more detailed cognitive assessment can inform which cognitive domains exert greater influence on the relationship between olfaction and depression.

The relationship between olfactory dysfunction and all-cause mortality and neurodegenerative disease risk are well-established findings; however, comparatively less is known about the relationship between olfaction and depression in late life. The coronavirus disease 2019 pandemic has hastened the need to understand the long-term neurologic and psychiatric consequences of olfactory deficits as the number of people at risk for chronic olfactory loss may grow. Our findings support prior work demonstrating an association between olfactory dysfunction and risk of increased depressive symptoms in late life. In particular, baseline olfactory dysfunction may confer independent risk beyond that of cognitive dysfunction and genetic risk for AD alone. Collectively, these findings underscore the need for a greater understanding of olfactory deficits in LLD and the demographic, cognitive and biological factors that may influence these relationships over time.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Concept and design: V.K., J.D., K.J., K.J.M. Manuscript writing: V.K., K.J., J.D. Data collection: E.M.S., K.Y. Data analysis: K.J. Data interpretation: V.K., J.D., K.J., H.C., K.A.W., K.J.M., R.S.M., W.D.B. Manuscript revisions and approval: All authors. The views and opinions expressed in this article are those of the authors and should not be construed to represent the views of the sponsoring organizations, agencies, or U.S. Government.

Conflict of Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study. F.R.L. reports serving as a volunteer board member of the nonprofit, Access HEARS, being a consultant to Frequency Therapeutics and Apple Inc, and being the director of a public health research center funded in part by a philanthropic donation from Cochlear Ltd. to the Johns Hopkins Bloomberg School of Public Health.

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