JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Association Between Olfactory Dysfunction and Mortality in US Adults

Janet S. Choi, MD, MPH; Sophie S. Jang, MS; Jeehong Kim, MD; Kevin Hur, MD; Elisabeth Ference, MD; Bozena Wrobel, MD

IMPORTANCE A study of olfactory dysfunction and mortality in a large national cohort will aid in better understanding their association when accounting for multiple relevant factors and possible underlying mechanisms.

OBJECTIVE To investigate the association of olfactory dysfunction with all-cause 5-year mortality in US adults.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included participants 40 years or older from the 2013-2014 National Health and Nutritional Examination Survey who had data on olfaction and mortality (n = 3503). Olfaction was assessed by self-report and objective test (8-odor Pocket Smell Test). Mortality was determined by linking with the National Death Index through February 24, 2019. Data were analyzed from July 1 to September 30, 2019.

MAIN OUTCOMES AND MEASURES Olfaction and 5-year mortality. Cox proportional regression models were used to examine the associations between olfaction and mortality while adjusting for demographics and medical comorbidities. Multivariate models were further adjusted for depression and cognitive assessments.

RESULTS Among the 3503 participants (1831 women [52.3%]; mean [SD] age, 59.0 [12.0] years), the prevalence of olfactory dysfunction was 13.5% (95% CI, 11.0%-16.0%) based on results of an objective smell test and 21.6% (95% CI, 18.9%-24.2%) based on self-report. Risk of mortality increased by 18% (95% CI, 7%-29%) per 1-point decrease in smell test score in a multivariate model. The association was significant among adults 65 years or older in association with binary (hazard ratio [HR], 1.95; 95% CI, 1.19-3.21) and linear (HR, 1.19; 95% CI, 1.08-1.31) measures of objective olfactory dysfunction, but not among adults aged 40 to 64 years. There was no association between self-reported olfactory dysfunction and mortality. The association between objective olfactory dysfunction and mortality remained after further adjusting for cognitive assessment battery and depression among older adults (HR, 1.18; 95% CI, 1.01-1.37).

CONCLUSIONS AND RELEVANCE These findings suggest that objective olfactory dysfunction is associated with increased mortality among older adults. In addition to its effect on quality of life, the association of olfactory dysfunction with mortality has implications for physical and cognitive health.

JAMA Otolaryngol Head Neck Surg. doi:10.1001/jamaoto.2020.3502
Published online October 22, 2020.

Invited Commentary

Author Affiliations: Caruso Department of Otolaryngology–Head and Neck Surgery, Keck School of Medicine of the University of Southern California, Los Angeles (Choi, Kim, Ference, Wrobel); Royal College of Surgeons in Ireland, Dublin (Jang); Department of Otolaryngology–Head and Neck Surgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Hur).

Corresponding Author: Janet S. Choi, MD, MPH, Caruso Department of Otolaryngology–Head and Neck Surgery, Keck School of Medicine of the University of Southern California, 1540 Alcazar St, Ste 204M, Los Angeles, CA 90033 (janet.choi@med.usc.edu).

Poor olfactory function has been directly implicated in malnutrition,[1] decreased safety,[2] and overall worse quality of life.[3] It is responsible for more than 200 000 physician visits per year, representing a significant public health burden.[4,5] Emerging evidence suggests that olfactory dysfunction is significantly associated with increased all-cause mortality among older adults.[4,6-11] Most notably, a recent study by Liu et al[12] examining community-dwelling older adults aged 71 to 82 years showed clear evidence that poor olfaction alone explains higher long-term mortality, particularly in individuals with excellent to good health at baseline. Liu et al[12] found the elevated risk of mortality of patients with poor olfaction was only partially explained by neurodegenerative disease, cardiovascular disease, and weight loss. Olfaction is emerging as an early indicator of brain aging that can be objectively measured with a relatively simple smell test in the clinical setting.

Choi et al[13] previously used the National Health and Nutrition Examination Survey (NHANES) to demonstrate that objectively measured olfactory dysfunction is associated with cognitive impairment independently of demographics and cardiovascular factors. Herein we further investigate the associations of olfactory dysfunction (measured by both objective smell test and self-report) with all-cause 5-year mortality in US adults 40 years or older, independently of cardiovascular factors, cognition, and depression.

Methods

Study Participants

NHANES is a database collected by the US Centers for Disease Control and Prevention to assess the nutritional and health status of the noninstitutionalized, civilian population in the United States. Each cohort in NHANES uses a complex sampling design with selective oversampling of low-income individuals and racial minorities.[14] Analyses accounting for the stratified, multistage probability sampling design yield results that are representative of the entire US population.[15] The analytic cohort for the present study consisted of 3503 individuals 40 years or older who had complete data on olfaction and mortality in the 2013-2014 NHANES. Olfaction was assessed by both an objective olfactory test and self-report. The study was exempt from institutional review board approval because the data had already been deidentified and are publicly available. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Olfactory Tests

Objective olfactory testing was assessed using the NHANES Pocket Smell Test (Sensonics International), which includes an 8-item scratch-and-sniff test. The 8 odorants include onion, soap, leather, smoke, grape, strawberry, chocolate, and natural gas. Participants were asked to identify each odorant from 4 alternative names. Normal olfaction was defined as being able to correctly identify at least 6 odors (score range, 0-8) as in previous literature.[16] Olfactory dysfunction was defined as having a score of 5 or less. Good test-retest reliability was observed from the NHANES olfaction protocol.[17]

Questionnaires on subjective olfaction were collected by the interviewer using the computer-assisted personal interviewing system. Self-reported olfactory dysfunction was defined as reporting a problem with smell in the past 12 months, worse sense of smell since 25 years of age, or phantosmia as previously defined.[18]

Cognition and Depression Measures

The cognitive function battery administered as per NHANES protocol consisted of the Animal Fluency Test,[19] assessments from the Consortium to Establish a Registry for Alzheimer Disease (CERAD),[20-22] and the Digit Symbol Substitution Test.[23] Depressive disorders were evaluated using the Patient Health Questionnaire.[24] Participants were categorized as having major depressive disorder if either of the initial questions addressing depressed mood was answered as "more than half the days" or "nearly every day" and the Patient Health Questionnaire score was at least 9 (possible range, 0-27, with higher scores indicating greater depressive symptoms). Details of each assessment are available in previously published studies examining the associations of olfactory dysfunction with cognition[13] and depression.[25]

Key Points

Question Is self-reported and/or objectively measured olfactory dysfunction associated with mortality when accounting for relevant factors among adults in the United States?

Findings In this nationally representative cohort study of 3503 adults 40 years or older, objectively measured olfactory dysfunction was significantly associated with increased all-cause 5-year mortality among older adults independent of demographics, cardiovascular comorbidities, depression, and cognition (18% increased risk per 1-point decrease in Pocket Smell Test score [score range, 0-8]). Self-reported olfactory dysfunction was not associated with mortality.

Meaning These findings suggest that objectively measured olfactory dysfunction is robustly associated with 5-year mortality among older US adults, and olfaction measured by objective smell test may be a useful indicator of health status in older adults.

Mortality

The National Center for Health Statistics has linked data collected from the NHANES surveys with death certificate records from the National Death Index.[26] Mortality was determined by probabilistic matching between NHANES data and death certificates through February 24, 2019.[27] For the NHANES survey, follow-up time has been calculated using person-months from the date of interview to the date of death or the end of the mortality period.

Other Study Measures

Demographic data and medical history were obtained during interviews. Self-reported race and ethnicity were grouped as White, Black, Hispanic, Asian, or other. Household income was collapsed into 5 categories and educational level into 3 categories as in **Table 1**. Medical history variables included hypertension, stroke, diabetes, smoking status, and cardiovascular disease (myocardial infarction, congestive heart failure, angina pectoris, or coronary artery disease). Other olfaction-related medical history data included ever having a broken nose or other serious injury to the face or the skull, persistent cold/flu for longer than 1 month in the past 12 months, ever having 2 or more sinus infections, and ever having a loss of consciousness because of a head injury.

Statistical Analysis

Data were analyzed from July 1 to September 30, 2019. Sample weights were used to account for the complex sampling design according to the NHANES analytic guidelines.[15] Baseline characteristics of the study participants were compared using the 2-tailed t test and Pearson χ^2 test. The association between various measures of olfactory dysfunction (binary self-reported, binary objectively measured olfactory dysfunction as defined above, and linear objectively measured olfactory dysfunction by a 1-point decrease in Pocket Smell Test score) and mortality was investigated using Cox proportional hazards regression models. Multivariate models were sequentially adjusted for age, demographics, cardiovascular risk factors, and olfaction-related medical history. In a subgroup of

Table 1. Demographic and Health-Related Characteristics of Participants 40 Years or Older With Objective Olfaction Testing Results and Self-report of Olfactory Dysfunction[a]

Characteristic	Participant group			
	Self-reported olfactory dysfunction		Objectively measured olfactory dysfunction (score ≤5)	
	Yes (n = 704)	No (n = 2799)	Yes (n = 626)	No (n = 2877)
Age, mean (SD), y	59.3 (12.4)	58.9 (12.0)	65.8 (12.2)	57.5 (11.5)
Female[b]	385 (54.7)	1446 (51.7)	260 (41.5)	1571 (54.6)
Race/ethnicity				
White	365 (51.8)	1194 (42.7)	248 (39.6)	1311 (45.6)
Black	119 (16.9)	603 (21.5)	151 (24.1)	571 (19.8)
Hispanic	152 (21.6)	617 (22.0)	141 (22.5)	628 (21.8)
Asian	44 (6.3)	338 (12.1)	77 (12.3)	305 (10.6)
Other	24 (3.4)	47 (1.7)	9 (1.4)	62 (2.2)
Educational level				
Less than high school	157 (22.3)	654 (23.4)	218 (34.9)	593 (20.6)
High school graduate	173 (24.6)	614 (22.0)	147 (23.5)	640 (22.3)
Some college or more	374 (53.1)	1529 (54.7)	260 (41.6)	1643 (57.1)
Refused/unsure	0	2 (<0.01)	1 (<0.01)	1 (<0.01)
Income, $				
<20 000	168 (23.9)	533 (19.0)	154 (24.6)	547 (19.0)
20 000-44 000	213 (30.3)	702 (25.1)	203 (32.4)	712 (24.7)
45 000-75 000	121 (17.2)	513 (18.3)	95 (15.2)	539 (18.7)
>75 000	164 (23.3)	798 (28.5)	116 (18.5)	846 (29.4)
Refused/unsure	38 (5.4)	253 (9.0)	58 (9.3)	233 (8.1)
Hypertension[b]	356 (50.6)	1273 (45.5)	348 (55.6)	1281 (44.5)
Cardiovascular disease[b,c]	114 (16.2)	295 (10.5)	110 (17.6)	299 (10.4)
Diabetes[b]	150 (21.3)	519 (18.5)	150 (24.0)	519 (18.0)
Stroke[b]	50 (7.1)	122 (4.4)	63 (10.1)	109 (3.8)
Smoking				
Never	311 (44.2)	1558 (55.7)	328 (52.5)	1541 (53.6)
Former	237 (33.7)	757 (27.1)	200 (32.0)	794 (27.6)
Current	156 (22.2)	483 (17.3)	97 (15.5)	542 (18.8)
Refused/unsure	0	1 (<0.01)	1 (<0.01)	0
Sinus infection	316 (44.9)	875 (31.3)	154 (24.6)	1037 (36.0)
Persistent cold symptoms	86 (12.2)	150 (5.4)	48 (7.7)	188 (6.5)
Previous head injury	336 (47.7)	153 (5.5)	86 (13.7)	403 (14.0)
Nasal or facial fracture	146 (20.7)	356 (12.7)	91 (14.5)	411 (14.3)

[a] Data are from 3503 participants in the 2013-2014 National Health and Nutrition Examination Survey. Measurements of olfactory dysfunction are described in the Methods section. Unless otherwise indicated, data are expressed as number (percentage) of participants. Percentages have been rounded and may not total 100.

[b] Considered binary.

[c] Includes any history of congestive heart failure, coronary artery disease, angina pectoris, or myocardial infarction.

adults younger than 65 years with available information on cognitive function and depression (n = 1022), a multivariate model was additionally adjusted for the cognitive assessment battery and major depressive disorder. STATA, version 16 (StataCorp LLC) was used for all analyses.

Results

The overall study cohort consisted of 3503 adults 40 years or older who participated in the 2013-2014 NHANES (1831 women [52.3%] and 1672 men [47.7%]; mean [SD] age, 59.0 [12.0] years). Unweighted participant characteristics are summarized in Table 1. The estimated prevalence of olfactory dysfunction was 21.6% (95% CI, 18.9%-24.2%) based on self-report and 13.5% (95% CI, 11.0%-16.0%) based on objective smell test results.

As of February 24, 2019, 105 individuals were determined to have died from the study cohort. The estimated 5-year mortality rate for adults aged 40 to 64 years was 1.2% (95% CI, 0.7%-2.0%), whereas for adults 65 years or older, it was 6.0% (95% CI, 4.5%-7.8%). Mortality rates were comparable between those who reported subjective olfactory dysfunction (2.5%; 95% CI, 2.0%-3.1%) and no subjective olfactory dysfunction (2.8%; 95% CI, 1.7%-4.8%) (**Table 2**). In contrast, those who had objectively measured olfactory dysfunction were found to have a higher mortality rate at 5.8% (95% CI, 3.9%-8.7%) compared with those who had normal olfactory function at 2.1% (95% CI, 1.5%-2.8%).

In the age-adjusted model, there was no association between self-reported olfactory dysfunction and risk of mortality (hazard ratio [HR], 1.12; 95% CI, 0.68-1.84) (**Table 3**). The binary measure of objective olfactory dysfunction was associated with 53% increased risk of mortality (HR, 1.53; 95% CI,

Table 2. Estimated All-Cause Mortality Rate by Subjective and Objective Olfactory Dysfunction at 5-Year Follow-up

Olfactory dysfunction	All-cause 5-y mortality rate, % (95% CI)
Self-reported	
No	2.5 (2.0-3.1)
Yes	2.8 (1.7-4.8)
Objectively measured[a]	
No	2.1 (1.5-2.8)
Yes (score ≤5)	5.8 (3.9-8.7)
Hyposmia (score 4 or 5)	6.0 (4.1-8.8)
Anosmia/severe hyposmia (score ≤3)	5.0 (2.2-11.2)

[a] Based on the 8-item National Health and Nutrition Examination Survey Pocket Smell Test findings (score range, 0-8).

1.02-2.30). When considering the NHANES Pocket Smell Test scores as a linear variable (score range, 0-8), a 1-point decrease in score was associated with a 19% increased risk of mortality (HR, 1.19; 95% CI, 1.08-1.30). In a multivariate model adjusting for demographics, comorbidities, and olfaction-related medical history, mortality risk was associated with linear measures of olfactory dysfunction (HR, 1.18; 95% CI, 1.07-1.29).

Subgroup analyses were performed by age group (middle-aged vs older adults). There was no association between mortality risk and subjective or objective measures of olfactory dysfunction among middle-aged adults. Among older adults, increased risk of mortality was observed in association with both binary measures (HR, 1.95; 95% CI, 1.19-3.21) and linear measures (HR, 1.19; 95% CI, 1.08-1.31) of objective olfactory dysfunction after adjusting for demographics, comorbidities, and olfaction-related medical history (Table 3).

Within a group of older adults who completed depression and cognitive assessments (n = 1022), an additional model including major depressive disorder (based on Patient Health Questionnaire score) and the cognitive assessment battery (including the Digit Symbol Substitution Test, Animal Fluency Test, and CERAD assessment) was constructed to examine whether the corresponding variables account for the association between olfactory dysfunction and mortality. The binary measure of objective olfactory dysfunction was associated with an estimated 61% increased risk of mortality (HR, 1.61; 95% CI, 0.98-2.66). A 1-point decrease in smell test score was associated with an estimated 18% increased risk of mortality (95% CI, 7%-29%) in older adults (HR, 1.18; 95% CI, 1.01-1.37) in this model with additional adjustment for depression and cognitive assessments.

Discussion

Objectively measured olfactory dysfunction was independently associated with increased risk of mortality at 5-year follow-up in this representative sample of US adults 40 years and older. Subgroup analysis by age demonstrated this association among adults 65 years or older but not among adults aged 40 to 64 years. These results were robust to analysis adjusting for other covariates, including demographics, cardiovascular disease, olfaction-related medical history, depression, and cognitive function. There was no association between self-reported olfactory dysfunction and mortality.

Our results are generally consistent with results from previous studies demonstrating association of olfactory dysfunction with increased mortality risk in older adults,[7-12,28-30] although the study population demographics, type of olfactory assessment test, and duration of follow-up vary substantially by report. Seven previous studies[7-12,28] have explored the association between objective olfactory dysfunction and mortality. Although most previous studies were recruited from regional community-dwelling older adults, the present study included a nationally representative sample of US adults with the largest sample size. One previous study[7] based on a nationally representative US sample from the National Social Life, Health and Aging Project (age range, 57-85 years) similarly demonstrated increased mortality risk among older adults with olfactory dysfunction. Our study had additional data on a validated measure of depression (Patient Health Questionnaire) and diverse measures of cognitive function and further included adults aged 40 to 65 years. One longitudinal cohort study from a city in northern Sweden[9] included a subgroup of middle-aged adults defined as 40 to 70 years. In that study, there was a significant association between objectively measured olfactory dysfunction (measured with the 13-item Scandinavian Odor Identification Test) and increased risk of mortality.[9] The discrepancy observed in our study is likely due to longer duration of follow-up (mean of 9.9 years) in the Swedish study compared with the 5-year follow-up data in the present study. Sensitivity analysis with adjustment of the age cutoff of 40 to 70 years did not show any association in our cohort. These findings suggest that olfactory function is not associated with 5-year mortality among middle-aged adults in the United States, but there may be an association with longer follow-up. Future longitudinal studies are needed to examine the role of olfactory dysfunction as a predictor of mortality at follow-up longer than 5 years.

Cognitive function was assessed as a potential mediator of the association between olfaction and mortality in a subgroup of older adults. Objective olfactory dysfunction is known to be associated with lower scores across various domains of cognitive function, including attention and executive function (Digit Symbol Substitution Test), verbal fluency (Animal Fluency Test), and memory (CERAD assessment).[13] In a multivariate model additionally adjusting for the cognitive assessment scores, a 1-point decrease in the smell test continued to be associated with higher risks of mortality similar to the findings from previous studies that have included a measure of cognitive function as a covariate (eg, the Mini-Mental State Examination,[9,10,12,28] the short Portable Mental Status Questionnaire,[7] or reported clinical diagnosis of dementia[8,28]). One previous study from a suburban Australian cohort[10] demonstrated that the link between olfaction and mortality was no longer significant after adjusting for the Mini-Mental State Examination score. Decline in cognitive function and its associated neurodegenerative diseases are likely one of several pathological processes that may account for the link between

Table 3. Cox Proportional Hazards Regression Adjusted Risk of 5-Year Mortality by Objective and Subjective Olfactory Dysfunction

Model[a]	HR (95% CI)		
	Self-reported olfactory dysfunction, binary[b]	Objectively measured olfactory dysfunction[b]	
		Binary	Linear (by 1-point decrease)
All participants			
Base plus age	1.12 (0.68-1.84)	1.53 (1.02-2.30)	1.19 (1.08-1.30)
Base plus demographics	1.06 (0.67-1.68)	1.45 (0.95-2.21)	1.18 (1.07-1.29)
Base plus demographics plus cardiovascular factors	0.97 (0.60-1.57)	1.45 (0.96-2.21)	1.17 (1.07-1.27)
Base plus demographics plus cardiovascular factors plus olfaction-related medical history	1.04 (0.63-1.72)	1.51 (0.98-2.33)	1.18 (1.07-1.29)
Adults aged 40-64 y			
Base plus age	0.95 (0.27-3.37)	0.41 (0.08-2.16)	1.10 (0.89-1.37)
Base plus demographics	0.90 (2.11-3.79)	0.37 (0.08-1.78)	1.06 (0.84-1.34)
Base plus demographics plus cardiovascular factors	0.67 (0.19-2.31)	0.32 (0.07-1.51)	1.05 (0.83-1.33)
Base plus demographics plus cardiovascular factors plus olfaction-related medical history	0.68 (0.28-1.67)	0.36 (0.08-1.55)	1.09 (0.85-1.41)
Older adults aged ≥65 y			
Base plus age	1.19 (0.77-1.83)	1.80 (1.13-2.83)	1.19 (1.09-1.29)
Base plus demographics	1.14 (0.76-1.70)	1.82 (1.10-3.03)	1.18 (1.08-1.30)
Base plus demographics plus cardiovascular factors	1.09 (0.73-1.61)	1.79 (1.08-2.96)	1.17 (1.07-1.29)
Base plus demographics plus cardiovascular factors plus olfaction-related medical history	1.16 (0.78-1.72)	1.95 (1.19-3.21)	1.19 (1.08-1.31)
Base plus demographics plus cardiovascular factors plus olfaction-related medical history plus MDD plus cognitive assessment battery[c]	1.15 (0.82-1.63)	1.61 (0.98-2.66)	1.18 (1.01-1.37)

Abbreviations: HR, hazard ratio; MDD, major depressive disorder.

[a] Demographic factors include age, sex, race, income, and educational level. Cardiovascular risk factors include hypertension, cardiovascular diseases, diabetes, stroke, and smoking. Olfaction-related medical history includes recent cold symptoms, previous sinus infection, previous head injury, and nasal or facial fracture. Cognitive assessment battery includes the Digit Symbol Substitution Test, the Animal Fluency Test, and the Consortium to Establish a Registry for Alzheimer Disease assessment. MDD was defined based on Patient Health Questionnaire scores.

[b] Measurements of olfactory dysfunction are described in the Methods section.

[c] Includes 1022 participants.

olfaction and mortality. Olfactory dysfunction has been identified to precede full clinical emergence of neurodegenerative diseases such as Alzheimer disease and Parkinson disease.[31-34] Previous pathologic studies[32,35,36] have shown that neurodegenerative markers in the olfactory tract (ie, α-synuclein, β-amyloid, and tau) are potentially involved in the early disease process. Another longitudinal cohort study in older adults[12] found that neurodegenerative diseases explain 22% of the increased risk of 10-year mortality among individuals with poor olfaction. Our findings demonstrating olfaction as associated with mortality independently of cognitive functioning imply that additional mechanisms underlie the association.

Several additional mechanisms have been proposed in the literature. First, a direct insult to the olfactory nerve, the only cranial nerve exposed to the environment, from a virus, bacteria, or toxins may be associated with injuries to other systemic organs, such as the central nervous, pulmonary, and cardiovascular systems, causing increased risk of mortality. Second, olfactory dysfunction may be a marker of advanced physiological aging, because poor recovery of olfactory functioning after environmental or internal insults is an indicator of poor cellular regeneration.[37-40] A recent study[29] has demonstrated increased interleukin 6 serum levels among older adults with olfactory dysfunction and suggested the increased inflammation as a common pathophysiological pathway that may be associated with hyposmia, frailty, and mortality. Olfactory dysfunction can also lead to malnutrition, unsafe food choices, and increased risks of accidents due to gas leaks and smoke.[12]

Depression is another potential mediator significantly associated with olfactory dysfunction and mortality. Olfactory bulb ablation in an animal model has been found to cause alterations in chemical and behavioral states that are similar to a depressed state.[41] On the other hand, depression can potentially cause elevated levels of inflammatory cytokines and glucocorticoids inhibiting neurogenesis of the olfactory system.[42-44] A large body of literature[45-48] has demonstrated the effect of depression on increased risk of mortality across various patient populations via worsening disease severity and development of additional comorbidities. A recent randomized clinical trial from Germany demonstrated that older adults with olfactory dysfunction who completed olfactory training for 5 months were found to report improved depressive symptoms.[49] These findings warrant future research to understand the effect of olfactory training on mortality in addition to quality of life and mental health. In our study, major depressive disorder was significantly associated with higher mortality risk, but olfactory dysfunction remained an independent risk factor associated with mortality in a multivariate model.

Our study findings suggest olfactory dysfunction as independently associated with mortality has clinical implications for physical, mental, and cognitive health, especially among

older adults. Adults with olfactory dysfunction are expected to be prone to malnutrition, because these individuals may have decreased appetite and ability to enjoy food, thereby leading to poor food intake.[1,50] Olfactory dysfunction may also prevent adults from recognizing life-threatening situations, such as a gas leak or a fire.[5] Olfactory dysfunction is known to be associated with poorer quality of life and higher prevalence of depressive symptoms.[3,25,50] In addition to olfactory dysfunction being suggestive of accelerated brain aging, it has been found to be an early factor associated with development of Alzheimer and Parkinson disease.[51,52] Detection of olfactory dysfunction, especially among older adults, suggests that further workup for malnutrition, depression, and neurodegenerative disease may be needed. Adults with known olfactory dysfunction should be more cautious of life-threatening situations because they are unable to smell danger signals in the household environment.[53]

Limitations

There are limitations to this study. First, various definitions of subjective and objective olfactory dysfunction and tests exist. We defined olfactory dysfunction a priori based on previous NHANES studies examining olfaction. The results may vary based on the definitions adopted. Second, despite adjusting for multiple major confounders and possible mediators, residual confounding by other environmental or medical factors cannot be completely ruled out. For example, the covariates obtained from cross-sectional data in this study limit assessment of potentially relevant information, such as changes in olfactory dysfunction (temporary vs permanent causes) or weight loss. In addition, the relatively smaller size of the subgroup analysis among older adults may have limited the power to detect significant associations in multivariate models. The specific causes of mortality were also not available in this study, which could have allowed for further analysis of a possible mechanism underlying the link between olfaction and mortality. Future studies are required to explore the basis of the association between olfactory dysfunction and mortality in a longitudinal study cohort at longer follow-up.

Conclusions

Objectively measured olfactory dysfunction is associated with an increased risk of 5-year all-cause mortality among older (≥65 years) but not middle-aged (40-64 years) US adults. Olfactory dysfunction was identified as independently associated with mortality after accounting for demographics, medical comorbidities, depression, and cognitive functioning.

ARTICLE INFORMATION

Accepted for Publication: August 14, 2020.

Published Online: October 22, 2020. doi:10.1001/jamaoto.2020.3502

Author Contributions: Drs Choi and Wrobel had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Choi, Kim, Hur, Ference, Wrobel.
Acquisition, analysis, or interpretation of data: Choi, Jang, Ference, Wrobel.
Drafting of the manuscript: Choi, Jang, Kim.
Critical revision of the manuscript for important intellectual content: Choi, Jang, Hur, Ference, Wrobel.
Statistical analysis: Choi, Jang.
Administrative, technical, or material support: Choi, Kim, Ference.
Supervision: Hur, Ference, Wrobel.

Conflict of Interest Disclosures: None reported.

Meeting Presentation: This paper was presented at the Triological Society Sections Meeting; January 23, 2020; Coronado, California.

REFERENCES

1. Gopinath B, Russell J, Sue CM, Flood VM, Burlutsky G, Mitchell P. Olfactory impairment in older adults is associated with poorer diet quality over 5 years. *Eur J Nutr*. 2016;55(3):1081-1087. doi:10.1007/s00394-015-0921-2

2. Santos DV, Reiter ER, DiNardo LJ, Costanzo RM. Hazardous events associated with impaired olfactory function. *Arch Otolaryngol Head Neck Surg*. 2004;130(3):317-319. doi:10.1001/archotol.130.3.317

3. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life—an updated review. *Chem Senses*. 2014;39(3):185-194. doi:10.1093/chemse/bjt072

4. Siegel JK, Wroblewski KE, McClintock MK, Pinto JM. Olfactory dysfunction persists after smoking cessation and signals increased cardiovascular risk. *Int Forum Allergy Rhinol*. 2019;9(9):977-985. doi:10.1002/alr.22357

5. Hoffman HJ, Rawal S, Li CM, Duffy VB. New chemosensory component in the US National Health and Nutrition Examination Survey (NHANES): first-year results for measured olfactory dysfunction. *Rev Endocr Metab Disord*. 2016;17(2):221-240. doi:10.1007/s11154-016-9364-1

6. 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(3):323-329. doi:10.1093/gerona/glt063

7. Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. Olfactory dysfunction predicts 5-year mortality in older adults. *PLoS One*. 2014;9(10):e107541. doi:10.1371/journal.pone.0107541

8. Devanand DP, Lee S, Manly J, et al. Olfactory identification deficits and increased mortality in the community. *Ann Neurol*. 2015;78(3):401-411. doi:10.1002/ana.24447

9. Ekström I, Sjölund S, Nordin S, et al. Smell loss predicts mortality risk regardless of dementia conversion. *J Am Geriatr Soc*. 2017;65(6):1238-1243. doi:10.1111/jgs.14770

10. Gopinath B, Sue CM, Kifley A, Mitchell P. The association between olfactory impairment and total mortality in older adults. *J Gerontol A Biol Sci Med Sci*. 2012;67(2):204-209. doi:10.1093/gerona/glr165

11. Wilson RS, Yu L, Bennett DA. Odor identification and mortality in old age. *Chem Senses*. 2011;36(1):63-67. doi:10.1093/chemse/bjq098

12. Liu B, Luo Z, Pinto JM, et al. Relationship between poor olfaction and mortality among community-dwelling older adults: a cohort study. *Ann Intern Med*. 2019;170(10):673-681. doi:10.7326/M18-0775

13. Choi JS, Hur K, Chow M, Shen J, Wrobel B. Olfactory dysfunction and cognition among older adults in the United States. *Int Forum Allergy Rhinol*. 2018;8(5):648-654. doi:10.1002/alr.22078

14. US Centers for Disease Control and Prevention. NHANES tutorials—module 2: sample design. Updated August 4, 2020. Accessed December 11, 2019. https://wwwn.cdc.gov/nchs/nhanes/tutorials/Module2.aspx

15. US Centers for Disease Control and Prevention. NHANES tutorials—module 3: weighting. Updated August 4, 2020. Accessed January 2, 2020. https://wwwn.cdc.gov/nchs/nhanes/tutorials/Module3.aspx

16. Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. *JAMA*. 2002;288(18):2307-2312. doi:10.1001/jama.288.18.2307

17. Rawal S, Hoffman HJ, Honda M, Huedo-Medin TB, Duffy VB. The taste and smell protocol in the 2011-2014 US National Health and Nutrition Examination Survey (NHANES): test-retest reliability and validity testing. *Chemosens Percept*. 2015;8(3):138-148. doi:10.1007/s12078-015-9194-7

18. Rawal S, Hoffman HJ, Bainbridge KE, Huedo-Medina TB, Duffy VB. Prevalence and risk factors of self-reported smell and taste alterations: results from the 2011-2012 US National Health and Nutrition Examination Survey (NHANES). *Chem*

Senses. 2016;41(1):69-76. doi:10.1093/chemse/bjv057

19. Stephan BC, Kurth T, Matthews FE, Brayne C, Dufouil C. Dementia risk prediction in the population: are screening models accurate? *Nat Rev Neurol*. 2010;6(6):318-326. doi:10.1038/nrneurol.2010.54

20. Gao S, Jin Y, Unverzagt FW, et al. Hypertension and cognitive decline in rural elderly Chinese. *J Am Geriatr Soc*. 2009;57(6):1051-1057. doi:10.1111/j.1532-5415.2009.02267.x

21. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), part I: clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989;39(9):1159-1165. doi:10.1212/WNL.39.9.1159

22. US Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey: 2013-2014 data documentation, codebook, and frequencies: Cognitive Funcioning (CFQ_H). Published March 2017. Accessed December 2, 2019. https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/CFQ_H.htm

23. Wechsler D. *Wechsler Adult Intelligence Scale–Fourth Edition (WAIS-IV)*. NCS Pearson; 2008.

24. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613. doi:10.1046/j.1525-1497.2001.016009606.x

25. Hur K, Choi JS, Zheng M, Shen J, Wrobel B. Association of alterations in smell and taste with depression in older adults. *Laryngoscope Investig Otolaryngol*. 2018;3(2):94-99. doi:10.1002/lio2.142

26. National Center for Health Statistics. Office of Analysis and Epidemiology 2015 public-use linked mortality file. Updated June 30, 2020. Accessed December 2, 2019. https://www.cdc.gov/nchs/data-linkage/mortality-public.htm

27. US Centers for Disease Control and Prevention. Public-use linked mortality files. Published February 24, 2019. Accessed December 2, 2019. ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/datalinkage/linked_mortality/

28. Schubert CR, Fischer ME, Pinto AA, et al. Sensory impairments and risk of mortality in older adults. *J Gerontol A Biol Sci Med Sci*. 2017;72(5):710-715.

29. Laudisio A, Navarini L, Margiotta DPE, et al. The association of olfactory dysfunction, frailty, and mortality is mediated by inflammation: results from the InCHIANTI Study. *J Immunol Res*. 2019;2019:3128231. doi:10.1155/2019/3128231

30. Leschak CJ, Eisenberger NI. The role of social relationships in the link between olfactory dysfunction and mortality. *PLoS One*. 2018;13(5):e0196708. doi:10.1371/journal.pone.0196708

31. 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(5):693-706. doi:10.1016/j.neurobiolaging.2006.11.014

32. Attems J, Walker L, Jellinger KA. Olfactory bulb involvement in neurodegenerative diseases. *Acta Neuropathol*. 2014;127(4):459-475. doi:10.1007/s00401-014-1261-7

33. Vasavada MM, Wang J, Eslinger PJ, et al. Olfactory cortex degeneration in Alzheimer's disease and mild cognitive impairment. *J Alzheimers Dis*. 2015;45(3):947-958. doi:10.3233/JAD-141947

34. 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(7):802-808. doi:10.1001/archpsyc.64.7.802

35. Attems J, Jellinger KA. Olfactory tau pathology in Alzheimer disease and mild cognitive impairment. *Clin Neuropathol*. 2006;25(6):265-271.

36. Jellinger KA, Attems J. Alzheimer pathology in the olfactory bulb. *Neuropathol Appl Neurobiol*. 2005;31(2):203. doi:10.1111/j.1365-2990.2004.00619.x

37. Watabe-Rudolph M, Begus-Nahrmann Y, Lechel A, et al. Telomere shortening impairs regeneration of the olfactory epithelium in response to injury but not under homeostatic conditions. *PLoS One*. 2011;6(11):e27801. doi:10.1371/journal.pone.0027801

38. Doty RL. The olfactory vector hypothesis of neurodegenerative disease: is it viable? *Ann Neurol*. 2008;63(1):7-15. doi:10.1002/ana.21327

39. Prediger RD, Aguiar AS Jr, Matheus FC, et al. Intranasal administration of neurotoxicants in animals: support for the olfactory vector hypothesis of Parkinson's disease. *Neurotox Res*. 2012;21(1):90-116. doi:10.1007/s12640-011-9281-8

40. Pagano SF, Impagnatiello F, Girelli M, et al. Isolation and characterization of neural stem cells from the adult human olfactory bulb. *Stem Cells*. 2000;18(4):295-300. doi:10.1634/stemcells.18-4-295

41. Lumia AR, Teicher MH, Salchli F, Ayers E, Possidente B. Olfactory bulbectomy as a model for agitated hyposerotonergic depression. *Brain Res*. 1992;587(2):181-185. doi:10.1016/0006-8993(92)90995-L

42. Kohli P, Soler ZM, Nguyen SA, Muus JS, Schlosser RJ. The association between olfaction and depression: a systematic review. *Chem Senses*. 2016;41(6):479-486. doi:10.1093/chemse/bjw061

43. Furtado M, Katzman MA. Examining the role of neuroinflammation in major depression. *Psychiatry Res*. 2015;229(1-2):27-36. doi:10.1016/j.psychres.2015.06.009

44. Yuan TF, Hou G, Arias-Carrion O. Chronic stress impacts on olfactory system. *CNS Neurol Disord Drug Targets*. 2015;14(4):486-491. doi:10.2174/1871527314666150429111356

45. Gathright EC, Goldstein CM, Josephson RA, Hughes JW. Depression increases the risk of mortality in patients with heart failure: a meta-analysis. *J Psychosom Res*. 2017;94:82-89. doi:10.1016/j.jpsychores.2017.01.010

46. Farooqi A, Khunti K, Abner S, Gillies C, Morriss R, Seidu S. Comorbid depression and risk of cardiac events and cardiac mortality in people with diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2019;156:107816. doi:10.1016/j.diabres.2019.107816

47. Bush DE, Ziegelstein RC, Tayback M, et al. Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. *Am J Cardiol*. 2001;88(4):337-341. doi:10.1016/S0002-9149(01)01675-7

48. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. *Psychol Med*. 2010;40(11):1797-1810. doi:10.1017/S0033291709992285

49. Birte-Antina W, Ilona C, Antje H, Thomas H. Olfactory training with older people. *Int J Geriatr Psychiatry*. 2018;33(1):212-220. doi:10.1002/gps.4725

50. Croy I, Negoias S, Novakova L, Landis BN, Hummel T. Learning about the functions of the olfactory system from people without a sense of smell. *PLoS One*. 2012;7(3):e33365. doi:10.1371/journal.pone.0033365

51. Braak H, Del Tredici K. Neuropathological staging of brain pathology in sporadic Parkinson's disease: separating the wheat from the chaff. *J Parkinsons Dis*. 2017;7(s1):S71-S85. doi:10.3233/JPD-179001

52. Marin C, Vilas D, Langdon C, et al. Olfactory dysfunction in neurodegenerative diseases. *Curr Allergy Asthma Rep*. 2018;18(8):42. doi:10.1007/s11882-018-0796-4

53. Van Regemorter V, Hummel T, Rosenzweig F, Mouraux A, Rombaux P, Huart C. Mechanisms linking olfactory impairment and risk of mortality. *Front Neurosci*. 2020;14:140. doi:10.3389/fnins.2020.00140