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Olfactory identification deficits and increased mortality in the community

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Potential Conflicts of Interest

D.P. Devanand has received consulting fees from AbbVie and Lundbeck. Richard Doty is President and major shareholder of Sensonics, Inc., a manufacturer and distributor of tests of taste and smell, including the UPSIT. Richard Doty has received publishing royalties from Cambridge University Press and Johns Hopkins University Press, and an honorarium from the University of Florida and lodging reimbursement as Chairperson of the Other Non-Motor Features of Parkinson's Disease working group of the Parkinson Study Group. He has received consulting fees from Pfizer, Inc., Acorda Therapeutics and several law offices. There are no other conflicts of interest.

Author Contributions

Drs. Devanand, Lee and Andrews had full access to all the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. Study Concept and Design: Devanand, Stern, Mayeux, Doty. Acquisition, analysis, or interpretation of data: Devanand, Manly, Masurkar, Schupf, Stern, Mayeux, Doty. Drafting of the manuscript: Devanand, Lee. Critical Revision of the manuscript for important intellectual content: Devanand, Manly, Masurkar, Schupf, Stern, Doty. Statistical analysis: Lee, Devanand, Andrews. Obtained funding: Devanand, Mayeux. Study supervision: Manly, Schupf, Stern, Mayeux.

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Abstract

Objective—To examine the association between odor identification deficits and future mortality in a multiethnic community cohort of older adults.

Methods—Participants were evaluated with the 40-item University of Pennsylvania Smell Identification Test (UPSIT). Follow-up occurred at 2-year intervals with information on death obtained from informant interviews and the National Death Index.

Results—During follow-up (mean 4.1 SD 2.6 years), 349 of 1169 (29.9%) participants died. Participants who died were more likely to be older ($p < 0.001$), male ($p < 0.001$), have lower UPSIT scores ($p < 0.001$), and have a diagnosis of dementia ($p < 0.001$). In a Cox model, the association between lower UPSIT score and mortality (Hazard Ratio 1.07 per point interval, 95%CI 1.05 to 1.08, $p<0.001$) persisted after controlling for age, gender, education, ethnicity, language, modified Charlson medical comorbidity index, dementia, depression, alcohol abuse, head injury, smoking, Body Mass Index, vision and hearing impairment (Hazard Ratio=1.05, 95%CI 1.03 to 1.07, $p<0.001$). Compared to the fourth quartile with the highest UPSIT scores, hazard ratios for mortality for the first, second, and third quartiles of UPSIT scores were 3.81 (95%CI 2.71 to 5.34), 1.75 (95%CI 1.23 to 2.50), and 1.58 (95%CI 1.09 to 2.30), respectively. Participant mortality rate was 45% in the lowest quartile of UPSIT scores (anosmia) and 18% in the highest quartile of UPSIT scores.

Interpretation—Impaired odor identification, particularly in the anosmic range, is associated with increased mortality in older adults even after controlling for dementia and medical comorbidity.

INTRODUCTION

The olfactory system is a unique sensory modality, largely because its receptors are exposed to the external environment. It is vulnerable to aging and the early pathology of several neurodegenerative diseases. Neurofibrillary tangles in the olfactory bulb and olfactory cortex are among the earliest signs of Alzheimer's disease (AD)[1] and Lewy bodies, which are the hallmark pathological indicators of Parkinson's disease (PD), are found throughout olfactory structures in early stage PD and related diseases.[2–4] Impaired performance on odor identification tests increase with age.[5] Impaired odor identification is associated with future cognitive decline in cognitively intact older adults,[6] and the transition from mild cognitive impairment (MCI) to AD.[6–7] In PD, olfactory dysfunction has been associated with

worsening gait,[8] neuropsychiatric complications,[9] and deficits in cardiac sympathetic functioning.[10]

Odor identification deficits may be associated with increased mortality in older adults,[11–12] but this finding is not firmly established. In a population-based study of 1,636 individuals, impaired odor identification on an 8-item smell test was associated with a 67% higher risk of all-cause mortality when compared to individuals without olfactory impairment.[13] Total serum cholesterol and cognitive impairment were assessed in the majority of study participants, and adjusting for either measure rendered the association non-significant.[13] Recently, a much higher risk (Odds Ratio OR 3.37; 95% CI 2.04, 5.57) for 5-year mortality was reported for poor olfactory performance, defined as anosmia based on a 5-item odor identification test, although this risk decreased after controlling for cognitive factors (OR 2.80; 95% CI 1.61, 4.86).[12] Limitations included the scoring of refusals to answer items as incorrect responses, which may have inflated the rate of anosmia, and the possibility that some participants may have had difficulty in comprehending the test instructions accurately.[14] Another community study found that poor performance on the 12-item Brief Smell Identification Test (B-SIT), which consists of a subset of UPSIT items, was associated with a 36% increase in mortality relative to individuals who performed well on the test. The authors suggested that the findings may reflect unidentified neurodegenerative disease.[11] However, longevity in Parkinson's disease is similar to the general population[15] and the decrease in longevity in patients with dementia is not large.[16]

The aforementioned literature on the association between odor identification deficits and increased mortality raises several unresolved issues with potential public health implications. These include the size of the effect and whether (a) it varies as a function of the degree of dysfunction, which is most accurately determined using longer and more reliable olfactory tests, (b) it simply reflects the increased risk of dementia in individuals with odor identification deficits, and (c) the increased risk remains after adjusting for medical disorders associated with heightened mortality risk. We addressed these questions in a multi-ethnic elderly community study in which odor identification deficits, measured by the 40-item UPSIT, have been associated with cognitive decline in cognitively intact older adults and the transition from mild cognitive impairment (MCI) to dementia during follow-up.[6, 17]

METHODS

Participants

A stratified random sample of 50% of all Medicare beneficiaries age 65 years and older, obtained from the Health Care Finance Administration, was recruited initially from a specific region of North Manhattan, New York.[18] This Washington Heights/Inwood Columbia Aging Project (WHICAP) cohort includes participants recruited originally in 1992 (approximately 25% of subjects) and a new cohort recruited between 1999 and 2001 (approximately 75% of subjects).[19] Key exclusion criteria were clinical stroke, Parkinson's disease based on standard diagnostic criteria,[20] atypical Parkinsonian syndrome diagnoses,[21,22] schizophrenia and other psychotic disorders.[19] At each visit, all participants received a standardized neuropsychological test battery that included measures of learning

and memory, orientation, abstract reasoning, executive function, language, and visuospatial ability. At all time-points, diagnoses of dementia, including AD dementia, were made at a consensus conference of neurologists and neuropsychologists, based on available clinical, cognitive and functional information but without UPSIT data.[6, 19] The Columbia University-New York State Psychiatric Institute Institutional Review Board approved the study protocol and informed consent was obtained from each participant.

Olfactory Testing

Odor identification testing was performed with the UPSIT, a highly reliable (test-retest r's > 0.90), sensitive and well-validated olfactory test.[23] The research technician administered the English or Spanish version of the UPSIT depending upon the participant's language preference. In the UPSIT, each of 40 common odorants is embedded in microcapsules located on separate pages of 10-page booklets. The participant scratches an odorant strip containing the microencapsulated odorant page, sniffs the emanated odor, and chooses the best answer from 4 items listed as multiple-choice. The total score ranges from 0 (no odors correctly identified) to 40 (all odors correctly identified). Since a subject must choose one of 4 choices for each odorant (i.e., the test is forced-choice), persons with no smelling ability score, on average, approximately 10 on the test. Participants who completed a minimum 38 of 40 UPSIT items are included in this report. For participants who completed only 38 or 39 items (1.3% of participants), a score of 0.25 was imputed for each missing item.[6]

The UPSIT was first administered between 2004 and 2006, identified as "baseline" for this report. Follow-ups occurred during 2006 – 2008 (first follow-up) and 2008 – 2010 (second follow-up).

Determination of mortality

When scheduling follow-up visits, mortality was ascertained and confirmed with family members and with review of the National Death Index.[24] Similar information was available for participants who died subsequent to scheduled follow-up visits. For deceased participants, the follow-up time was defined from baseline assessment to the date of death. For all other participants, the last available follow-up was the censoring date.

Demographics and Risk Factors for Mortality

Age, gender, race/ethnicity, years of education, and language of UPSIT administration (English or Spanish) were included as covariates in all analyses. Participant interview was used to rate vision and hearing impairment, and items for chronic liver disease, chronic obstructive pulmonary disease, arthritis, peptic ulcer disease, myocardial infarction, diabetes, peripheral vascular disease, stroke, hypertension, and systemic malignancy. In order to derive a modified version of the Charlson Index of Comorbidity[25], all of these items received a weight of 1 except for chronic liver disease and systemic malignancy that were each weighted 2. Current or past history of depression, history of head trauma, history of smoking, alcohol abuse, body mass index (BMI) and apolipoprotein E genotype were also evaluated.

Statistical Analyses

Statistical analyses were conducted with SAS Version 9.3 (SAS Institute, Cary, North Carolina). Distributions and group differences in demographic and clinical variables between participants who died or survived were examined by χ^2-tests and general linear models.

The association of the UPSIT score with mortality based on maximum available follow-up was assessed with Cox proportional hazard models[26] (PROC PHREG in SAS) with the Efron method to address ties. The proportional hazards assumption was evaluated by testing a non-zero slope in linear regression models of the Schoenfeld residuals as a function of event time. All models satisfied the assumption. The initial model included the UPSIT score alone. We then added demographic covariates, and in further analyses also included the covariates of modified Charlson comorbidity index, CES-D (depression) score, and dichotomized measures for dementia, vision impairment, hearing impairment, alcohol abuse, history of smoking, history of head trauma, and BMI. In follow-up analyses, we examined the individual comorbidity items instead of the comorbidity index.

Finally, the association of the UPSIT score with mortality within 5 years was assessed by logistic regression analysis (PROC LOGISTIC SAS). The analysis strategy was the same as that for the proportional hazard models.

RESULTS

Baseline Demographic and Clinical Measures

At initial evaluation, 1169 participants met inclusion/exclusion criteria. During follow-up (mean 4.1 SD 2.6 years, range 0–9.8 years), 349 (29.9%) participants died and 820 (70.2%) survived. Among the 349 participants who died, 227 (65%) died within 5 years.

As shown in Table 1, participants who subsequently died were older ($p < 0.001$) and more likely to be male ($p < 0.001$), had a history of smoking ($p=0.012$), had lower UPSIT scores ($p < 0.001$), had visual impairment ($p=0.0017$), and were more likely to be diagnosed with dementia ($p < 0.001$). Deceased participants were more likely to have heart disease ($p < 0.001$), including myocardial infarction ($p < 0.001$), and diabetes ($p=0.006$).

The association between olfactory identification deficits and mortality was evaluated in Cox proportional hazards models (Table 2). In the model that included the UPSIT score alone, the risk of death increased by 6.8% for each point decrement in the UPSIT score (Hazard Ratio HR = 1.068 per point interval, 95% confidence interval [CI]: 1.053, 1.083, $p < 0.001$). The association between lower UPSIT score and mortality persisted (HR=1.049, 95% CI 1.030, 1.068, $p < 0.001$) after controlling for demographic variables, medical comorbidity index (HR=1.140, 95% CI 1.058,1.229, $p < 0.001$), baseline dementia (HR=1.712, 95% CI 1.141, 2.568, p=0.009), history of smoking (HR=1.337, 95% CI 1.083, 1.750, p=0.009), vision impairment (HR=1.632, 95% CI 1.145, 2.326, p=0.007) and hearing impairment, alcohol abuse, depression, head injury, and BMI, each of which were non-significant (Table 2). Figure 2 shows that a person with a score of 15/40 (solid line, 10th percentile) was nearly two and a half times more likely to die than a person with a score of 34/40 (dotted line, 90th

percentile; HR=2.477, 95% CI 1.768, 3.469) after adjustment for demographic variables and all other covariates. Similar results were found for 5-year mortality using logistic regression analyses (Table 3).

Among the participants who were followed, the proportion diagnosed with dementia did not differ significantly between those who died (11.8%) and those who remained alive (9.65%, χ^2=1.10, p=0.294). During follow-up, 19 participants were diagnosed with Parkinson's disease (9 died during follow-up), 5 were diagnosed with Parkinson's disease plus dementia (3 died during follow-up), and 5 were diagnosed with Lewy body dementia (5 died during follow-up). There were 97 participants with dementia at baseline (94 of whom did not develop a Parkinson's-related diagnosis, 43 died during follow-up) and an additional 110 participants who were diagnosed with dementia at the last available follow-up. Among these 110 participants, 100 were diagnosed as dementia without a Parkinson's-related diagnosis (65 probable AD, 12 dementia with stroke, 19 AD with other concomitant disease, 1 combined systems disease, 1 other dementia, 2 cause unknown), and 29 participants died during follow-up.

After excluding participants with baseline or follow-up diagnoses of dementia, the results remained very similar in Cox regression analyses that examined the association between baseline UPSIT scores and mortality during follow-up (UPSIT score: HR 1.067 per point interval, 95%CI 1.050, 1.085; UPSIT score with all covariates: HR 1.054, 95%CI 1.034, 1.075; all p's < 0.0001). Further, after excluding participants with baseline or follow-up diagnoses of dementia and follow-up diagnoses of Parkinson's related syndromes, the results remained similar (UPSIT score: HR 1.063, 95% CI 1.040, 1.081; UPSIT score with all covariates: HR 1.053, 95% CI 1.032, 1.074; all p's < 0.0001).

BMI was weakly associated with UPSIT scores (r=0.09, p=0.0017), unrelated to mortality, and was not significant when included as a covariate in additional Cox regression analyses (Table 2). Apolipoprotein E ε4 genotype, a risk factor for Alzheimer's disease, was not significant in similar analyses.

We divided the subjects into four groups using UPSIT score quartiles: [0–20], [20–26], [26–31] and [31–40]. The association with mortality was strongest in participants in the lowest quartile of UPSIT scores in which 45% of participants died during follow-up compared to 18% in the highest quartile of UPSIT scores (Figure 1). Compared to the fourth quartile with the highest UPSIT scores, the HRs for mortality for the first, second, and third quartiles of UPSIT scores were 3.81 (95% CI 2.71, 5.34), 1.75 (95% CI 1.23, 2.50), and 1.58 (95% CI 1.09, 2.30), respectively. To further evaluate the lowest quartile group that demonstrated the greatest mortality risk, we subdivided this group by UPSIT scores. Without adjusting for covariates, the subgroup with the lowest UPSIT score of 0 to 10 was associated with the highest mortality rate in the total sample (HR 4.10, 95% CI 2.32, 7.27), and this risk did not differ significantly from those with UPSIT scores of 11 to 20 (HR 3.77, 95% CI 2.67, 5.32).

DISCUSSION

In this multi-ethnic elderly community cohort, odor identification deficits, as measured by a well-validated test of olfactory function, were associated with increased mortality both in survival analyses with maximum available follow-up and in logistic regression analyses limited to 5-year follow-up. This association was attenuated by age, gender, medical comorbidity, dementia and other known risk factors for mortality, but it remained statistically significant in analyses that controlled for these and other relevant, available covariates. The mortality rates associated with the modified Charlson index of comorbidity and specific medical conditions included in the index were consistent with those reported in other elderly community cohorts,[27] suggesting wide applicability of this study's findings.

Unlike prior studies, our findings are based on a 40-item smell test that provides a well-defined and extended continuum of degrees of smell function. Nonetheless, after controlling for potential confounding risk factors, our estimate of the likelihood of someone dying who has poor olfaction (HR 2.43; 95% CI 1.797, 3.271 for the 10th percentile compared to the 90th percentile of UPSIT scores) is similar to that reported with a brief smell test in another epidemiological study (OR, 2.80; 95% CI 1.61, 4.86).[12] In our study, there was a progressive increase in mortality risk over quartiles of diminishing UPSIT scores. The upper limit of UPSIT scores for the lowest quartile was 20, which is slightly higher than the score of less than 18 out of 40 that indicates anosmia (inability to smell) in the general population.[28] This finding is consistent with another report of anosmia, defined as a score of 0 or 1 in a 5-item odor identification test, being associated with a comparable increase in mortality.[12] Our estimate of risk is considerably higher than that reported in another study[11] which found that individuals with a B-SIT score in the lowest decile were 1.36 times more likely to die than individuals in the highest decile, and does not concur with another report that showed that the higher risk of mortality in persons with poor smell function was not significant after controlling for the effects of cognitive function or total cholesterol levels.[13] The discrepant findings may reflect differences across studies: exclusion of PD patients in some samples, including our own, though excluding participants who were diagnosed with Parkinson's, AD plus PD and Lewy body dementia during follow-up did not alter the findings; slightly varying age ranges; baseline health variances, the olfactory tests that were employed, the criteria for defining olfactory dysfunction, and the specific cognitive, medical, and related factors that were controlled. Our study, as well as others,[11–12] suggests that dementia cannot fully explain the observed association between odor identification deficits and the increased likelihood of future mortality. This is despite the fact that odor identification deficits are related to some degree to postmortem pathological markers of several neurodegenerative disorders (e.g., AD, PD, Lewy body disease) and to future cognitive decline, even in cognitively intact subjects.[6, 29–30] Vision and hearing impairment did not alter the association between odor identification deficits and mortality, indicating that this finding cannot be explained by sensory loss more broadly. Of note, gender, education, and particularly age can affect odor identification test performance and need to be taken into account in its interpretation. In our previous report in a clinical sample of patients with MCI with average age of 67 years and 16 years of education,[31] mean UPSIT scores

were in the low 30's compared to the mid-20's in this community cohort with an average age above 80 years with mean 10 years of education.

In the general population, loss of odor identification ability can be related to altered nasal engorgement, increased propensity for nasal disease, cumulative damage to the olfactory epithelium from viral infections, decreased levels of mucosal metabolizing enzymes, cribriform plate foramina ossification, loss of odor-specific selectivity of receptor cells, changes in neurotransmitter and neuromodulator systems, head trauma, and neuronal expression of aberrant proteins related to neurodegenerative diseases.[28] Some proportion of olfactory losses reverses over time, although less so in older cohorts.[32] Twin studies performed in older populations suggest that heritability coefficients decline with age, suggesting that genetic variance is overtaken by environmental and other age-related changes within the olfactory pathways.[33]

In our cohort, apolipoprotein E ε4 genotype,[34] head trauma, and alcohol abuse did not affect the association between odor identification deficits and increased mortality. One possible explanation is that with individuals with these risk factors may not survive into old age, and therefore may be under-represented in our elderly cohort. From an evolutionary perspective, deficits in odor identification in rodents and canines and other mammals that have excellent odor identification abilities would be expected to increase mortality based on their diminished ability to evade predators and choose the right type of food source. In humans it is possible that odor identification deficits may lead to unhealthy food choices or malnutrition or an increased risk of accidents such as gas fires and explosions. A disproportionate number of elderly die in accidental gas poisonings and explosions every year, some of which can be attributed to smell loss.[35] In one study, nearly half of older adults were unable to detect the smell of the warning agent added to natural gas at the concentration level dictated by safety standards.[36] In another study, 37% of 445 patients presenting to a smell and taste center with complaints of smell loss reported having experienced a serious olfaction-related hazardous event at some point in their lives, as compared to only 19% of those with no such impairment. Included were cooking-related incidents (45%), ingestion of spoiled food (25%), lack of ability to detect leaking natural gas (23%), and inability to smell a fire (7%).[37]

Other factors are known to be associated with mortality risk. In addition to age and gender, these include taste dysfunction,[38] use of dentures,[39] number of teeth,[40] hearing deficits,[41] mobility problems,[42] pain,[42] self-related health problems,[40] blood pressure variability,[44] and psychological distress.[45] It has been suggested that olfactory dysfunction may be related to slowed cellular regeneration (olfactory cells regenerate throughout life) or possibly as a marker of cumulative toxic environmental exposures during the aging process.[12] There clearly remains a need for larger studies in which a broader range of factors and their combinations are included in the predictive models.

There were some limitations to this study. In this cohort, the results supported the use of the UPSIT in both English and Spanish-speaking individuals after age, gender and education were taken into account. Further, the UPSIT has 14 translated versions for different languages and cultures. Nonetheless, modifications of test items may be needed for specific

cultures, e.g., 34 out of 40 culturally relevant UPSIT items were used effectively in an Italian clinical study.[46] Participants with Parkinson's disease and atypical Parkinsonian syndromes were excluded. These patients are known to have odor identification deficits years before the onset of motor symptoms[47] that may be due to Lewy body inclusions in the olfactory bulb and primary olfactory cortex.[48–50] However, after accounting for participants who developed Parkinson's or related syndromes during follow-up, the association between olfactory impairment and mortality remained. Further, in patients with Parkinson's disease, longevity over the course of the first 10 years after diagnosis (average age of onset 60 years) is not different from the general population and mortality increases only slightly with disease duration beyond 10 years.[15] We controlled for age, gender, ethnicity, education, medical comorbidity, depression, hearing and vision impairment and other risk factors in our cohort, but information from medical records was not available in this epidemiological study that relied on participant interviews. All studies, including ours, that have examined the association between odor identification deficits and mortality have evaluated and followed older adults. From a public health standpoint, it will be important to ascertain if odor identification deficits in young to middle-aged samples are also associated with increased mortality over the individual's lifespan.

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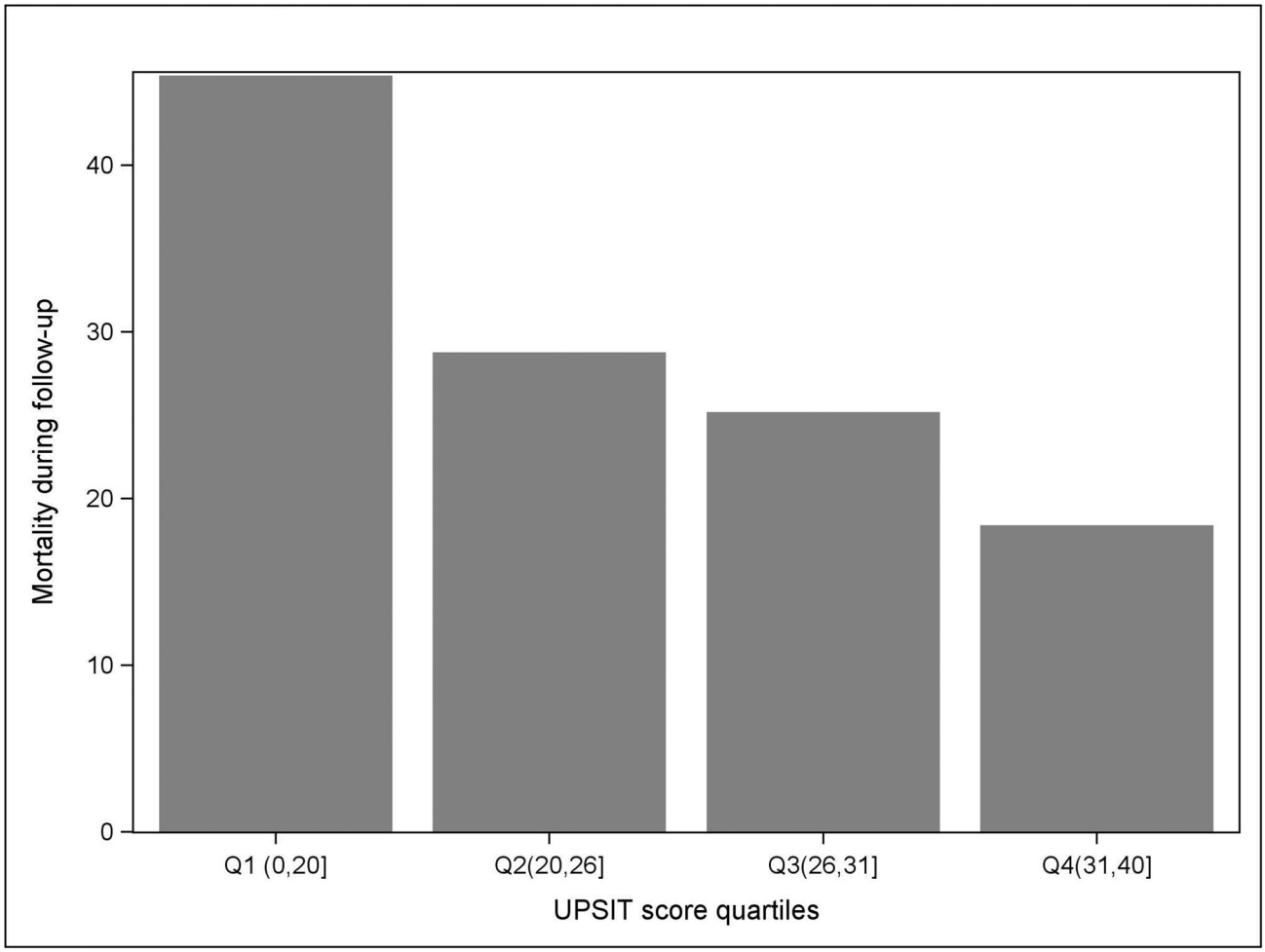

Figure 1.

Mortality rates during follow-up by baseline UPSIT score quartiles.

UPSIT (range 0–40) quartile scores: [0–20], [20–26], [26–31] and [31–40]. For maximum available follow-up, the UPSIT score was significantly associated with mortality (chisq=54.25, $p < .001$). For study participants, mortality rates were 45.36% in the highest quartile, 28.75% and 20.63% in the next two quartiles, respectively, and 18.39% in participants with the lowest quartile of UPSIT scores as shown in the four bar charts in the figure.

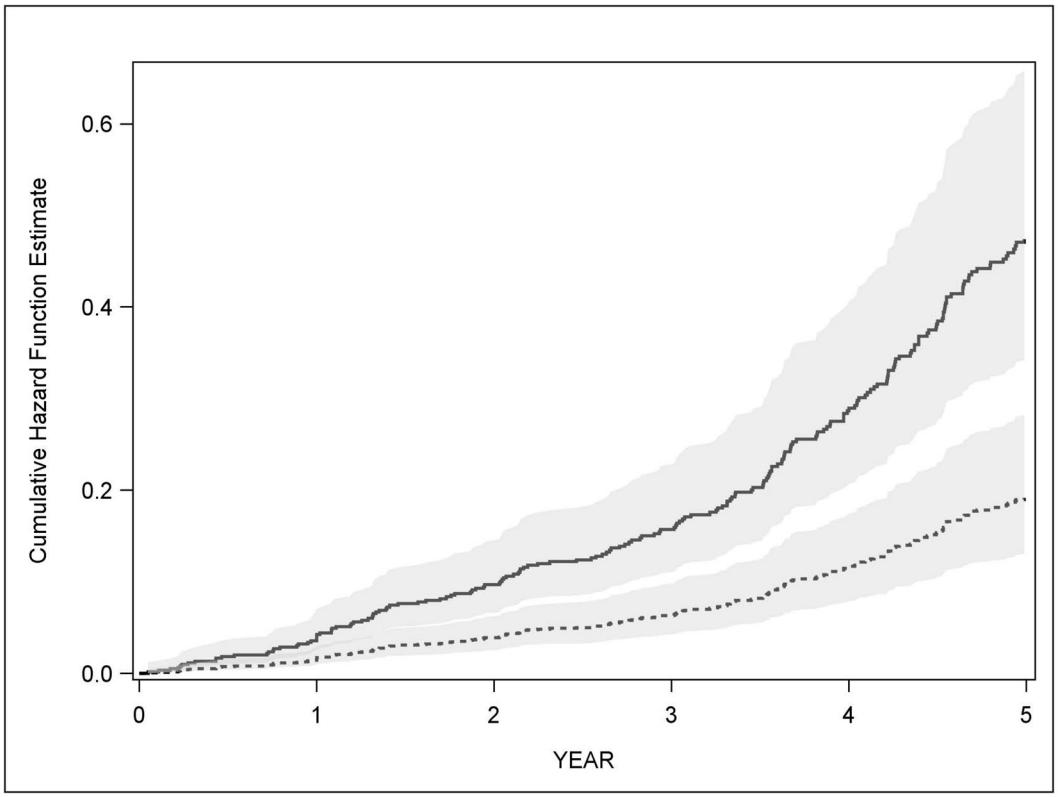

Figure 2.

Cumulative Hazard Function for mortality during follow-up for participants with baseline UPSIT scores at the 10th and 90th percentiles in the sample (total n=1169).

Cumulative hazard function from Cox proportional hazard regression analyses for baseline UPSIT scores at the 10th percentile (UPSIT score=15, solid line) and the 90th percentile (UPSIT score=34, dotted line) with death as the outcome, adjusted for the following covariates: age, gender, education, race/ethnicity, language of test administration, Charlson comorbidity index, dementia status, depression, head injury, alcohol use, BMI, smoking history. The gray shaded areas are the 95% confidence intervals of the cumulative hazard functions.

Table 1

Baseline demographic and clinical features classified by the outcome of mortality during follow-up.

Variable	5 year follow-up					Maximum available follow-up					Total sample (n=1169)	
	ALIVE (n=942, 80.58%)		DECEASED (n=227, 19.42%)		p-value	ALIVE (n=820, 70.15%)		DECEASED (n=349, 29.85%)		p-value		
	Mean	SD	Mean	SD		Mean	SD				Mean	SD
UPSIT score (range 0–40)	25.80	7.03	22.60	7.61	<.001	26.23	6.94	22.72	7.39	<.001	25.18	7.26
Age in years	80.39	5.55	83.42	6.52	<.001	80.11	5.42	83.02	6.38	<.001	80.98	5.87
Education in years	10.38	4.87	10.24	5.02	0.69	10.33	4.88	10.41	4.96	0.80	10.35	4.90
Sex (% male)	28.2		41.0		<.001	27.2		39.0		<.001	30.7	
Race/ethnicity (%)												
White	29.0		30.8		0.89	28.2		32.1		0.53	29.3	
Black	30.5		30.4			30.5		30.4			30.5	
Hispanic	39.2		37.0			39.9		36.1			38.8	
Other	1.4		1.8			1.5		1.4			1.5	
Apolipoprotein E ε4	24.2		25.7		0.64	24.81		23.6		0.66	24.5	
Dementia (%)	6.3		16.8		<.001	6.5		12.6		<.001	8.3	
Charlson Comorbidity Index	2.68	1.52	3.06	1.69	0.001	2.64	1.50	3.03	1.68	<.001	2.76	1.56
Stroke	8.5		14.1		0.010	8.6		12.0		0.065	9.6	
Heart Disease	25.6		34.1		0.013	24.0		35.6		<.001	27.5	
Myocardial infarction	8.1		15.6		<.001	6.8		15.9		<.001	9.2	
Peripheral vascular disease	20.4		24.3		0.192	20.2		23.3		0.23	21.2	
Hypertension	72.0		71.8		0.96	72.3		71.1		0.66	71.9	
Diabetes	21.0		24.2		0.29	19.5		26.7		0.006	21.6	
Chronic Obs. Pulm. Disease	13.7		20.3		0.013	14.2		16.9		0.23	15.0	
Arthritis	66.6		67.4		0.825	66.6		67.2		0.83	66.8	
Peptic ulcer disease	15.0		15.4		0.86	15.1		14.9		0.95	15.1	
Chronic liver disease	1.1		2.2		0.169	1.1		1.7		0.39	1.3	
Systemic malignancy	20.0		22.6		0.39	19.0		23.9		0.063	20.5	
Current depression (%)	13.2		15.9		0.51	12.8		15.8		0.38	13.7	
Past depression (%)	70.0		66.5			69.8		68.2			69.3	

Variable	5 year follow-up					Maximum available follow-up					Total sample (n=1169)	
	ALIVE (n=942, 80.58%)		DECEASED (n=227, 19.42%)		p-value	ALIVE (n=820, 70.15%)		DECEASED (n=349, 29.85%)		p-value		
	Mean	SD	Mean	SD		Mean	SD				Mean	SD
History of head Injury (%)	9.5		8.4		0.61	8.7		10.6		0.29	9.2	
Alcohol abuse (%)	9.3		10.0		0.79	8.9		10.0		0.54	9.2	
History of smoking (%)	48.0		35.7		<.001	43.6		35.8		0.012	38.1	
Basal Metabolic Index (BMI)	27.10	5.72	27.91	5.77	0.065	27.32	5.80	27.94	5.75	0.101	27.76	5.77
Vision impairment %	18.89		9.10		<.001	15.48		9.08		0.002	10.98	
Hearing impairment %	6.22		4.06		0.159	6.34		3.69		0.045	4.48	

Table 2

Proportional Hazard Models for baseline UPSIT score association with mortality during maximum follow-up.

	Variables		Estimate	S.E.	P-value	HR	95% CI	
Model 1 UPSIT only	**UPSIT**		−0.07	0.01	<.001	1.068	1.053	1.083
Model 2 UPSIT with Demographic and Other Covariates	**UPSIT**		−0.05	0.01	<.001	1.049	1.030	1.068
	Age		0.07	0.01	<.001	1.071	1.047	1.095
	Education		0.01	0.02	0.713	1.006	0.974	1.039
	Race/Ethnicity	**Black**	−0.05	0.16	0.733	0.948	0.698	1.288
		Hispanic	0.10	0.35	0.778	1.104	0.556	2.193
		Other	−0.06	0.52	0.909	0.942	0.339	2.621
	Gender	**Male**	0.42	0.13	0.001	1.529	1.180	1.981
	Language	**Spanish**	−0.37	0.35	0.294	0.692	0.347	1.377
	Comorbidity index		0.13	0.04	<.001	1.140	1.058	1.229
	Dementia	**Yes**	0.54	0.21	0.009	1.712	1.141	2.568
	Depression	**Current**	0.16	0.17	0.352	1.172	0.839	1.637
		Past	0.07	0.17	0.688	1.072	0.765	1.501
	Head Injury	**Yes**	−0.11	0.19	0.579	0.900	0.619	1.308
	Alcohol abuse	**Yes**	−0.03	0.20	0.891	0.973	0.659	1.438
	BMI		−0.01	0.01	0.230	0.988	0.968	1.008
	Smoking	**Yes**	0.32	0.12	0.009	1.377	1.083	1.750
	Hearing	**Impaired**	−0.07	0.26	0.796	0.934	0.557	1.566
	Vision	**Impaired**	0.49	0.18	0.007	1.632	1.145	2.326

UPSIT: 40-item University of Pennsylvania Smell Identification Test. Comorbidity Index: Modified Charlson Comorbidity Index. BMI: Body Mass Index.

Table 3

Logistic regression analyses for the association of baseline UPSIT score with mortality by 5-year follow-up.

	Variables		Estimate	S.E.	P-value	OR	95% CI	
Model 1: UPSIT only	**UPSIT**		−0.06	0.01	<.001	1.062	1.041	1.083
Model 2 UPSIT with Demographic and Other Covariates	**UPSIT**		−0.04	0.01	0.002	1.041	1.015	1.068
	Age		0.08	0.02	<.001	1.085	1.051	1.121
	Education		0.04	0.02	0.117	1.037	0.991	1.086
	Race/Ethnicity	**Black**	−0.12	0.23	0.591	0.884	0.564	1.386
		Hispanic	0.32	0.51	0.536	1.375	0.501	3.771
		Other	0.22	0.64	0.726	1.250	0.359	4.355
	Gender	**Male**	0.64	0.19	<.001	1.891	1.305	2.738
	Language	**Spanish**	−0.31	0.52	0.553	0.735	0.265	2.034
	Comorbidity index		0.18	0.06	<.001	1.201	1.076	1.340
	Dementia	**Yes**	0.55	0.29	0.057	1.727	0.983	3.033
	Depression	**Current**	0.11	0.25	0.664	1.117	0.679	1.835
		Past	0.14	0.23	0.558	1.147	0.725	1.814
	Head Injury	**Yes**	−0.32	0.31	0.314	0.729	0.395	1.348
	Alcohol use	**Yes**	0.06	0.29	0.828	1.065	0.605	1.875
	BMI		0.00	0.02	0.768	0.996	0.966	1.026
	Smoking	**Yes**	0.49	0.18	0.006	1.628	1.153	2.299
	Vision	**Impaired**	0.36	0.25	0.150	1.440	0.877	2.363
	Hearing	**Impaired**	−0.20	0.39	0.602	0.817	0.383	1.744

UPSIT: 40-item University of Pennsylvania Smell Identification Test. Comorbidity Index: Modified Charlson Comorbidity Index. BMI: Body Mass Index.