

Research Article

Sensory Impairments and Risk of Mortality in Older Adults

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Abstract

Background: Sensory impairments increase with age and the majority of older people will experience a sensory impairment if they live long enough. However, the relationships of hearing, visual, and olfactory impairments with mortality are not well understood.

Methods: Epidemiology of Hearing Loss Study participants ($n = 2,418$) aged 53–97 years (mean = 69 years) were examined in 1998–2000 and hearing, visual acuity, and olfaction were measured. Participants were followed for mortality for up to 17 years (mean = 12.8 years). Cox proportional hazards models were used to assess the association between prevalent sensory impairments and the 15-year cumulative incidence of death.

Results: A total of 1,099 (45.4%) of participants died during the follow-up period. In age- and sex-adjusted Cox models, the risk of mortality was higher among participants with one (hazard ratio [HR] = 1.40, 95% confidence interval [CI] = 1.19, 1.64) or two or more (HR = 2.12, 95% CI = 1.74, 2.58) sensory impairments than among participants with no sensory impairments. Olfactory impairment at baseline was significantly associated with mortality (HR = 1.28, 95% CI = 1.07, 1.52) after adjusting for age, sex, sensory comorbidities, cardiovascular risk factors and disease, cognitive impairment, frailty, subclinical atherosclerosis, and inflammatory marker levels ($n = 1,745$). Hearing and visual impairment were not associated with mortality after adjusting for subclinical atherosclerosis and inflammation.

Conclusion: Olfactory impairment, but not hearing or visual impairment, was associated with an increased risk of mortality. These results suggest that olfactory impairment may be a marker of underlying physiologic processes or pathology that is associated with aging and reduced survival in older adults.

Keywords: Aging—Hearing loss—Longitudinal studies—Mortality—Olfactory dysfunction—Visual impairment

The human senses of sight, sound, and smell are elegant sensorineural systems that allow us to experience, interpret, and navigate our environment. As with all biological systems, these sensorineural systems are likely susceptible to the effects of physiological dysregulation and disease leading to declines in function with age (1). Whereas the trajectory of physiological aging varies from person to person owing to genetics, environment, and health, data from prevalence studies clearly demonstrate that sensory impairments increase with age and the majority of older people will experience a sensory impairment if they live long enough (2–4).

The causes of age-related sensory dysfunctions are likely multifactorial and heterogeneous and some dysfunction may be due to systemic factors that affect both sensory systems and mortality risk. The most common causes of death in the United States among people 65 years and older are heart disease, cancer, chronic lower

respiratory disease, stroke, Alzheimer's disease, and diabetes (5). Many of these conditions have several risk factors, including subclinical atherosclerosis and inflammation, in common with risk factors for hearing impairment (HI), visual impairment (VI), or olfactory impairment (OI) (4,6–13). Sensory impairments may be good markers of aging and therefore also markers of mortality risk. However, previous studies have been inconsistent and the relationships of HI, VI, and OI with mortality are not well understood.

Findings from previous studies of HI and mortality have been mixed with modest significant associations in minimally adjusted models that are attenuated when additional mortality risk factors are included (14–16). VI, though much less common than HI, has been significantly associated with mortality in several studies (17–20) though in some studies (17,18), these associations were limited to younger participants or men. There have been fewer studies of olfaction and

mortality but they have more consistently reported olfactory dysfunction to be associated with an increased risk of mortality (21–23) with the exception of one study (24), where the association was no longer significant after adjusting for cognitive impairment.

Inconsistencies among previous studies may be partly due to the lack of adjustment for sensory comorbidities and residual confounding from other mortality risk factors. It is important to consider all three senses in analyses as they commonly co-occur and occur more frequently together than if they were independent (25). Although a few studies have included two sensory impairments in their analyses (26,27), to our knowledge, there have been no studies evaluating measures of HI, VI, and OI and mortality. In addition, previous studies have varied in the mortality risk factors for which they adjusted and have not included measures of subclinical atherosclerosis or inflammation, important risk factors for mortality (28,29).

As a longitudinal study, with hearing, vision, and olfaction measured at multiple time points and 15 years of follow-up, the Epidemiology of Hearing Loss Study (EHLS) is uniquely qualified to assess the associations of both prevalent and incident sensory impairments and mortality while controlling for sensory and other health comorbidities. We hypothesized that (a) HI, VI, and OI at baseline would be independently associated with mortality and, (b) these associations would be attenuated after adjustment for other sensory impairments and mortality risks, and (c) these associations would no longer be significant after adjusting for subclinical atherosclerosis and inflammatory marker levels. Additionally, we explored the prospective association of the development of sensory impairment(s) among people without existing sensory impairments at baseline and the risk of mortality over 10 years.

Methods

The EHLS is a population-based longitudinal study of sensory function and aging in Beaver Dam, WI. A private census of Beaver Dam was conducted in 1987 to determine the population of people 43–84 years living in the community and these individuals were invited to participate in the Beaver Dam Eye Study (BDES, 1988–1990, $n = 4,926$, 83% of eligible) (3). In 1993, participants in the BDES were invited to participate in the EHLS (1993–1995, $n = 3,753$, 83% of eligible), concurrent with the BDES 5-year examination (2). Subsequent EHLS and BDES examinations of the study population were conducted concurrently approximately every 5 years and participation was $\geq 80\%$ of survivors at each examination (2,7,12,30,31). The baseline for this study was the 1998–2000 EHLS examination, which was the first examination that included a measure of olfaction. During each examination, data were obtained by trained examiners following similar standardized protocols. Approval for this research was obtained from the Health Sciences Institutional Review Board of the University of Wisconsin and informed consent was obtained from all participants prior to each examination.

Hearing was measured in a sound-treated booth using pure-tone air- (0.5, 1, 2, 3, 4, 6, 8 kHz) and bone conduction (0.5, 2, 4 kHz) audiometry following the guidelines of the American Speech-Language-Hearing Association (30,31). Masking was used as necessary. Mild or greater HI was defined as a pure-tone average of the air conduction thresholds at 0.5, 1, 2, and 4 kHz greater than 25 dB Hearing Level in either ear (30).

Olfaction was measured using the eight-item San Diego Odor Identification Test, a reliable test with good test–retest agreement for OI (4,32). The test score is the number of odorants correctly identified (0–8) after two trials. Mild or greater OI was defined as identifying fewer than six odorants correctly (4,9).

Visual acuity was measured at the concurrent BDES examination using the Early Treatment Diabetic Retinopathy Study charts R1 and 2 modified for a 2-m distance (3). Best-corrected visual acuity was measured with participants wearing trial frames constructed according to their measured refraction (Humphrey 530 refractor, Allergan Humphrey, San Leandro, CA). Mild or greater VI was defined as best-corrected visual acuity of 20/40 or worse in the better eye (3,12).

All-cause mortality was the outcome for all analyses. Information on vital status was obtained through annual contact by telephone with the participant, or if unable to reach the participant, with contacts provided by the participant at the most recent examination, and by monitoring obituaries in the local newspaper.

Covariates were selected to be included in these analyses based on previous associations with sensory impairments or mortality. High-resolution B-mode carotid artery ultrasound images of the far and near walls of the common, internal, and bifurcation were obtained (AU4, Esaote North America Inc., Indianapolis, IN) on the right and left sides to measure carotid intima plus media thickness (IMT), a marker of subclinical atherosclerosis (33). The mean of the 12 walls was calculated for the IMT (33). High-sensitivity C-reactive protein (CRP) and interleukin-6 (IL-6) were measured on non-fasting blood samples obtained at baseline and stored at -80°C until assay at the Advanced Research and Diagnostic Laboratory (University of Minnesota, Minneapolis, MN). CRP was measured using a latex-particle enhanced immunoturbidimetric method (Roche Diagnostics, Indianapolis, IN) and IL-6 was measured using quantitative sandwich enzyme immunoassay techniques (QuantiKine High Sensitivity kit; R&D Systems, Minneapolis, MN). The laboratory interassay coefficient of variation was 4.5% for CRP and 11.7% for IL-6 (6).

Blood pressure was measured using Random Zero mercury sphygmomanometers and hypertension was defined as a diagnosis of high blood pressure with current antihypertensive medication use or a measured systolic blood pressure of more than or equal to 140 mm Hg or a measured diastolic blood pressure of more than or equal to 90 mm Hg. Diabetes was defined as a diagnosis of diabetes, or a diagnosis of suspected diabetes with current treatment, or a measured glycosylated hemoglobin more than 8% (or hemoglobin A1C of $\geq 6.5\%$). The Mini-Mental State Examination was administered and cognitive impairment was defined as a score of less than 24 or a self- or proxy-report of Alzheimer's disease or dementia (34,35). A frailty score for each participant was calculated from gait time (time to walk a measured course at usual pace), chair stand (standing up from a chair without using their arms), peak expiratory flow rate using the mini-Wright meter, and grip strength in the dominant hand using a hand dynamometer (36). Height and weight were measured and body mass index was calculated (kg/m^2).

Demographic, lifestyle, and medical history were obtained by interview; self-reported medical history included a history of cardiovascular disease (myocardial infarction, angina, stroke or transient ischemic attack), cancer (excluding nonmelanoma skin), and Alzheimer's disease. Participants were asked about smoking history (current, past, or never smoker), history of alcohol abuse (ever a time consistently drank four or more alcoholic drinks per day), and frequency of exercise (times per week: none, one to two, three or more).

Statistical Analyses

Analyses were conducted using SAS version 9.4 software (SAS Institute Inc., Cary, NC). All-cause mortality was modeled in days from participant's entry at baseline through June 30, 2015. Age- and sex-adjusted Kaplan–Meier survival curves were constructed to estimate the probability of survival by the number of prevalent sensory

impairments present at baseline. An age- and sex-adjusted Cox proportional hazards model was used to estimate the risk of mortality by the number of prevalent sensory impairments. A series of Cox proportional hazards models were used to assess the association between prevalent sensory impairments and the 15-year cumulative incidence of death. Each set of models included sensory impairments analyzed both individually and together. The first set of models were adjusted for age and sex; in the second set, demographic, behavioral, cognitive, and cardiovascular disease factors were added; and in the final comprehensive models, IMT and inflammatory markers were added. Additionally, sensitivity analyses among participants without baseline impairment were also modeled to evaluate the association of incident sensory impairments at the second visit and the 10-year cumulative incidence of mortality. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed using the parameter estimates and their standard errors.

Results

There were 2,418 participants at the baseline (1998–2000) examination with hearing, olfaction, and vision data of whom 1,099

(45.5%) died during the follow-up period. Mean follow-up time was 12.8 years with a maximum of 17 years. The mean age at baseline was 69 years (range 53–97) and 42% were male (Table 1). HI (50%) and OI (24%) were more common than VI (3%) which was rare. Among those with a HI, 37% also had OI or VI or both. In contrast, 73% of those with OI and 86% of those with a VI also had a HI. Only 8% of those with VI and 26% of those with OI impairment did not have another sensory impairment. The risk of mortality was significantly higher among participants with one (HR = 1.40, 95% CI = 1.19, 1.64) or two or more (HR = 2.12, 95% CI = 1.74, 2.58) sensory impairments than among participants with no sensory impairments in age- and sex-adjusted Cox models (Figure 1).

HI (HR = 1.34, 95% CI = 1.15, 1.55), OI (HR = 1.53, 95% CI = 1.34, 1.75), and VI (HR = 1.36, 95% CI = 1.06, 1.74) were associated with mortality in individual age- and sex-adjusted Cox models. All three sensory impairment estimates were slightly attenuated when modeled together (Table 2, Model 1). There were 1,745 participants with complete covariate data. Participants without complete covariate data were more likely to be older, female, have a sensory impairment, and to have died (Supplementary Table 1). Age- and sex-adjusted models were repeated in those

Table 1. Baseline Characteristics of Epidemiology of Hearing Loss Study Participants by Survival Status

Baseline Characteristic	All (<i>n</i> = 2,418)	Survived (<i>n</i> = 1,309)	Died (<i>n</i> = 1,099)
Age (y)	68.6	63.6	74.5
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Men	1,021 (42.2)	534 (40.5)	487 (44.3)
Women	1,397 (57.8)	785 (59.5)	612 (55.7)
Hearing impairment			
No	1,209 (50.0)	871 (66.0)	338 (30.8)
Yes	1,209 (50.0)	448 (34.0)	761 (69.2)
Olfactory impairment			
No	1,842 (76.2)	1,161 (88.0)	681 (62.0)
Yes	576 (23.8)	158 (12.0)	418 (38.0)
Visual impairment			
No	2,339 (96.7)	1,314 (99.6)	1,025 (93.3)
Yes	79 (3.3)	5 (0.4)	74 (6.7)
Number of sensory impairments			
None	1,050 (43.4)	793 (60.1)	257 (23.4)
1	911 (37.7)	442 (33.5)	469 (42.7)
≥2	457 (18.9)	84 (6.4)	373 (33.9)
Education (y)			
<12	433 (17.9)	144 (10.9)	289 (26.3)
12	1,172 (48.5)	663 (50.3)	509 (46.4)
13–15	394 (16.3)	232 (17.6)	162 (14.8)
16+	417 (17.3)	279 (21.2)	138 (12.6)
Smoking history			
Never	1,153 (47.7)	660 (50.0)	493 (44.9)
Past	1,021 (42.2)	531 (40.3)	490 (44.6)
Current	244 (10.1)	128 (9.7)	116 (10.6)
Cardiovascular disease			
No	1,965 (81.5)	1,194 (90.7)	771 (70.4)
Yes	447 (18.5)	122 (9.3)	325 (29.7)
Cancer			
No	2,132 (88.2)	1,228 (93.1)	904 (82.3)
Yes	286 (11.8)	91 (6.9)	195 (17.7)
Hypertension			
No	983 (40.7)	656 (49.7)	327 (29.8)
Yes	1,433 (59.3)	663 (50.3)	770 (70.2)
Cognitive impairment			
No	2,246 (93.4)	1,280 (97.3)	966 (88.5)
Yes	160 (6.7)	35 (2.7)	125 (11.5)

with complete covariate data (Table 2, Model 2) and results were similar.

After adjusting for additional demographic and behavioral factors, biomarkers, and comorbid conditions, only OI remained significantly associated with mortality over the following 17 years in both the individual sensory (HR = 1.30, 95% CI = 1.09, 1.55) and the multiple sensory models (HR = 1.28, 95% CI = 1.07, 1.52; Table 2, Model 4). HI was attenuated but remained significant in the initial multiple sensory multivariable model (Table 2, Model 3) but VI did not and neither HI nor VI were significant in the comprehensive model that included IMT, IL-6, and CRP (Table 2, Model 4; HI: HR = 1.17, 95% CI 0.97, 1.40; VI: HR = 1.36, 95% CI = 0.92, 2.01). Findings were similar in models stratified by age or gender, and when using cut-points more consistent with moderate or greater impairment (>40 dB hearing level either ear for HI; visual acuity 20/50 or worse in the better eye for VI; less than four odors identified for OI; results not shown).

In sensitivity analyses, there were 699 participants without any sensory impairment at baseline (1998–2000) with complete follow-up data 5 years later (2003–2005). Among these participants, the development of HI, VI, or OI at follow-up was not associated with an increased risk of mortality in the following 10 years in either the age- and sex-adjusted or fully adjusted models (Table 3).

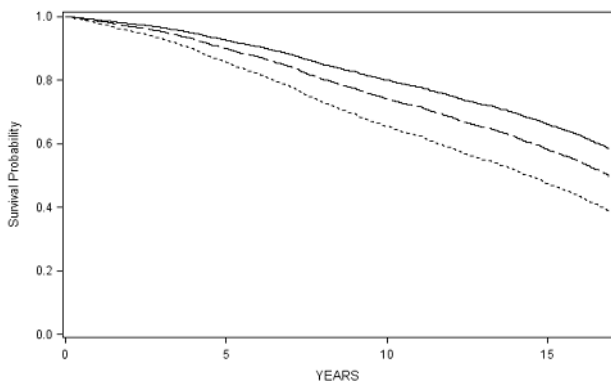


Figure 1. Age- and sex-adjusted probability of survival by number of sensory impairments in the Epidemiology of Hearing Loss Study. Solid line = no sensory impairment; dashed line = one sensory impairment; dotted line = two or more sensory impairments.

Discussion

In this longitudinal population-based study of older adults with multiple sensory measures, only OI was associated with an increased risk of mortality over the 17 years of follow-up in prevalent analyses. Neither HI nor VI was significant after adjusting for subclinical atherosclerosis and inflammatory marker levels, important potential confounders not included in previous studies. In the incident analyses in the subset of participants with no sensory impairments at baseline, development of a HI, VI, or OI were not associated with an increased risk of mortality in the following 10 years.

Our prevalent OI results are consistent with several previous studies that reported associations between olfactory dysfunction and increased risk of mortality (21–23) but differs from another study where the association with OI was no longer significant after controlling for cognitive impairment (24). To our knowledge, our study of sensory impairments and mortality is the only study that included objective, standardized measures of hearing, vision, and olfaction. When modeled together with other mortality risk factors, OI remained significantly associated with mortality while HI and VI were attenuated and no longer significant after adjusting for IMT and inflammatory marker levels. Whereas inflammation and IMT have previously been associated with HI and ocular pathology (6,8,13,37), inflammatory marker levels were not associated with OI, and IMT was only associated in those younger than 60 years, in a previous study in this population (10). As it is unlikely that OI is a direct cause of mortality, our results suggest there may be residual confounding or that OI may be a marker of different pathological processes or more advanced physiological aging than HI or VI. Also, it is possible that the odor identification test may be more cognitively demanding than the hearing or vision tests and therefore may be a more sensitive marker of brain aging. OI predicted the 5-year incidence of cognitive impairment in this population in a previous study (35). Poorer performance on odor identification tests has been associated with pathological markers of neurodegeneration in the brain (38,39). A higher density of neurofibrillary tangles in the entorhinal cortex and the CA1/subiculum region of the hippocampus in one study (38) and a thinner entorhinal cortex among those with elevated cortical amyloid in another (39). Olfactory dysfunction could also be an indicator of a decline in neurogenesis in the olfactory epithelium or bulb or the hippocampus. Neurogenesis is thought to occur throughout the lifespan in these areas and the processes responsible for this decline, or the loss of plasticity associated

Table 2. Sensory Impairment at Baseline and Risk of Mortality in the Epidemiology of Hearing Loss Study

	n	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)	
Modeled individually									
Hearing		1.34 (1.15, 1.55)		1.37 (1.15, 1.63)		1.23 (1.02, 1.47)		1.19 (0.99, 1.42)	
Olfactory	2,418	1.53 (1.34, 1.75)	1,745	1.52 (1.29, 1.79)		1.32 (1.11, 1.57)		1.30 (1.09, 1.55)	
Visual		1.36 (1.06, 1.74)		1.72 (1.19, 2.49)		1.51 (1.03, 2.21)		1.42 (0.96, 2.10)	
Modeled together									
Hearing		1.32 (1.13, 1.53)		1.32 (1.11, 1.58)		1.21 (1.01, 1.45)		1.17 (0.97, 1.40)	
Olfactory	2,418	1.50 (1.31, 1.72)	1,745	1.46 (1.24, 1.73)		1.29 (1.08, 1.54)		1.28 (1.07, 1.52)	
Visual		1.26 (0.98, 1.61)		1.57 (1.09, 2.27)		1.44 (0.98, 2.10)		1.36 (0.92, 2.01)	

Note: Model 1: all participants with complete sensory data, adjusted for age and sex. Model 2: participants with complete sensory and covariate data, adjusted for age and sex. Model 3: adjusted for Model 2 plus education, hypertension, diabetes, cardiovascular disease, cancer, cognitive impairment, frailty, smoking, exercise, body mass index, and alcohol. Model 4: adjusted for Model 3 plus intima media thickness, C-reactive protein, and interleukin-6. CI = confidence interval; HR = hazard ratio.

Table 3. Risk of Mortality by Incident Sensory Impairment at 5-y Follow-up Among Epidemiology of Hearing Loss Study Participants ($n = 699$) Without Sensory Impairment at Baseline

	Age and Sex Adjusted	Fully Adjusted
	HR (95% CI)	HR (95% CI)
Modeled individually		
Hearing	1.03 (0.68, 1.57)	0.80 (0.51, 1.25)
Olfactory	1.30 (0.79, 2.16)	1.39 (0.80, 2.44)
Visual	0.74 (0.27, 2.03)	0.62 (0.21, 1.79)
Modeled together		
Hearing	1.00 (0.65, 1.53)	0.77 (0.49, 1.20)
Olfactory	1.33 (0.80, 2.21)	1.47 (0.84, 2.59)
Visual	0.70 (0.25, 1.96)	0.54 (0.18, 1.58)

Note: Fully adjusted models include: age, sex, education, hypertension, diabetes, cardiovascular disease, cancer, cognitive impairment, frailty, smoking, exercise, body mass index, alcohol, intima media thickness, C-reactive protein, and interleukin-6. CI = confidence interval; HR = hazard ratio.

with it, could theoretically affect both olfactory function and also be related to the trajectory of aging and mortality (40).

In contrast to the prevalent OI results, incident OI was not significantly associated with an increased risk for 10-year mortality. This negative finding with the incident analyses suggests OI is not causally involved in risk of mortality. However, it remains possible that the shorter follow-up time of 10 years is not sufficient to detect an effect.

Our results, similar to other studies, do not support a direct association between HI and mortality. Although HI was associated with mortality in the multivariable models adjusting for many cardiovascular disease risk factors and cognitive impairment, this association did not remain significant after adjusting for IMT and inflammation, risk factors for both HI and mortality (6,8,28,29). Two previous studies of HI and mortality also reported significant findings in multivariable-adjusted models but found the associations mediated by cognition and walking ability (14,15). Another study reported moderate HI was associated with risk of mortality in an age-adjusted model but the results were not significant after including sex, race, and education in the model (16). In contrast, the AGES-Reykjavik Study did find a significant association between HI and also dual sensory impairment (HI and VI) with mortality in adjusted models but this finding was in men and not women, and they did not adjust for IMT or inflammation (26).

Similar to HI, VI was also not directly associated with mortality in the comprehensive prevalent multivariable models or in the incidence analyses in the current study. VI was previously found to be associated with decreased survival overall in the BDES population but not in stratified models where associations were only significant in men or those less than 65 years and models were not adjusted for frailty, IMT, or inflammation (17). VI was uncommon in the current study population and only 8% of participants with VI did not have sensory comorbidity. The Blue Mountains Eye Study and the AGES-Reykjavik Study found only dual sensory impairment (HI and VI), but not VI alone, associated with increased mortality risk (26,27). Previous studies with significant findings that did not include other sensory measures may have had bias due to residual confounding.

The strengths of this study include being a large, population-based, longitudinal study with a high retention rate and over 15 years of follow-up, standardized, objective, measures of hearing, vision, and olfaction, and measurement of carotid IMT and CRP, IL-6, and

many other mortality risk factors. Limitations include not knowing the cause of death which prohibited analyses based on type of mortality and no information was available on dietary intake. Additionally, olfaction was not measured until the second EHLS examination which reduced follow-up to approximately 15 years for prevalent analyses and 10 years for the incident analyses and this reduced the number of participants without any sensory impairment available for the incident analyses which may have limited our ability to detect associations.

Conclusion

In this population-based study of older adults with measures of hearing, vision, and olfaction, only OI was associated with an increased risk of mortality. These results suggest that OI may be a marker of underlying physiologic processes or pathology that is associated with physiological aging and reduced survival in older adults.

Supplementary Material

Supplementary material can be found at: <http://biomedgerontology.oxfordjournals.org/>

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Conflict of Interest

None of the authors have any conflicts.

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