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Research Article

Multiple Sensory Impairment Is Associated With Increased Risk of Dementia Among Black and White Older Adults

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Abstract

Background: Few studies have examined impairment in multiple senses (multisensory impairment) and risk of dementia in comparison to having a single or no sensory impairment.

Methods: We studied 1,810 black and white nondemented participants from Health, Aging, and Body Composition (Health ABC) Study aged 70–79 years at enrollment. Sensory impairment was determined at our study baseline (Year 3–5 of Health ABC) using established cut points for vision (Bailey–Lovie visual acuity and Pelli–Robson contrast sensitivity test), hearing (audiometric testing), smell (12-item Cross-Cultural Smell Identification Test), and touch (peripheral nerve function tests). Incident dementia over 10 years of follow-up was based on hospitalization records, dementia medications, or at least 1.5 SD decline in Modified Mini-Mental State Examination score (race-specific). Cox proportional hazard models with adjustment for demographics, health behaviors, and health conditions evaluated the relationship between risk of dementia and increasing number of sensory impairments.

Results: Sensory impairments were common: 28% had visual impairment, 35% had hearing loss, 22% had poor smell, 12% had touch insensitivity; 26% had more than two impairments, and 5.6% had more than three sensory impairments. Number of impairments was associated with risk of dementia in a graded fashion ($p < .001$). Compared to no sensory impairments, the adjusted hazard ratio was 1.49 (95% CI: 1.12, 1.98) for one sensory impairment, 1.91 (95% CI: 1.39, 2.63) for two sensory impairments, and 2.85 (95% CI: 1.88, 4.30) for more than three sensory impairments.

Conclusions: Multisensory impairment was strongly associated with increased risk of dementia. Although, the nature of this relationship needs further investigation, sensory function assessment in multiple domains may help identify patients at high risk of dementia.

Keywords: Dementia, Cognitive Aging, Sensory impairment, Epidemiology.

Sensory impairments, including hearing, vision, and olfaction, affect up to 65% of older adults (1). Several prospective studies have found that sensory impairments are individually associated with increased risk of mortality (2,3) and dementia (4–10). Sensory impairment may be a marker of underlying neurodegeneration (6), or a consequence of the same disease processes as those affecting cognition, such as cerebrovascular disease (11–13). Alternatively, sensory impairments may accelerate cognitive decline, such as through the effects of sensory impairment on social isolation, depression, or physical activity (14,15).

Prior research has typically focused on individual sensory impairments, however, some studies have found that dual deficits in hearing and visual loss may have a greater impact on health outcomes than a single sensory deficit (2,4,7). Research on vision, hearing, and olfaction found that increasing number of impairments was associated with mortality (3), and each impairment was associated with cognitive decline when modeled together (7,9). This suggests there may be additive effects of multiple impairments in sensory function (eg, multisensory impairment) on dementia. However, other work suggests

that multisensory impairment may represent a single underlying global aging process (1,16,17). Additional research may help clarify the impact of multisensory impairment on dementia risk. Few studies have incorporated other often unstudied senses such as smell and touch, examined differences by sex and race, or examined combined versus individual effects of sensory impairments on dementia risk.

The objective of this study was to examine whether multisensory impairment was associated with higher risk of dementia in comparison to a single or no sensory impairment. We studied black and white older adults in the Health, Aging, and Body Composition (Health ABC) Study and explored differences in the association by race and sex. Multisensory impairment was based on objective measures of hearing, vision, olfaction, and touch (specifically lower extremity peripheral sensory nerve function). We also tested whether individual measures were associated with dementia risk.

Methods

Participants

Health ABC is a longitudinal cohort study of black and white men and women aged 70–79 years at enrollment (18). A total of 3,075 participants were recruited 1997–1998 from a random sample of Medicare-eligible adults living within selected Zip codes in Pittsburgh, Pennsylvania, and Memphis, Tennessee. To be eligible, participants had to be able to walk one fourth mile and climb 10 stairs without difficulty, to report no difficulties in activities of daily living, to be free from life-threatening cancers, and to plan to remain in the study area for at least 3 years. Participants were followed for up to 16 years with annual clinical examinations, 6 month phone calls, and medical records review for major incident health events. The study was approved by the institutional review boards at each clinical site and the study coordinating center, all participants gave signed informed consent.

The current analysis focused primarily on 1,810 participants with nonmissing hearing, vision, smell, and touch assessments between Health ABC Year 3 (1999–2000) and Year 5 (2001–2002). Participants were nondemented at Year 5 (2001–2002) and had at least one follow-up visit or phone interview. The following participants were excluded: 294 participants missing one or more sensory assessments; 232 participants with prevalent dementia; and 739 participants missing covariate data. To maximize the sample in analyses of individual sensory impairments, we focused on 2,100 participants with at least one sensory function test. Health ABC participants not included in this analysis tended to be older and a higher percentage were black, were apolipoprotein (APOE) $\epsilon 4$ positive, had not completed high school, and had a history of hypertension, diabetes, and depression (all χ^2 p s < .001).

Multisensory Impairment

Hearing, vision, smell, and touch were each measured once between Health ABC Study Years 3–5 (considered the baseline for this analysis). As there are no established scores for quantifying multisensory impairment, we created dichotomous categories for each sensory function using established clinical or previously published upon cut points. The number of impairments was summed (score 0–4).

Visual function was measured binocularly with usual corrective lenses in Year 3 with the Bailey–Lovie distance visual acuity test (19), with values converted to Snellen equivalents, and Pelli–Robson contrast sensitivity test (20). Visual impairment was defined based on previously used cut points as current visual acuity of 20/40 or worse

(participants generally had high visual acuity) (21) or log contrast units 1.55 or less (7,22). Participants were also asked if they had a history of cataracts, age-related macular degeneration, glaucoma, and/or retinopathy. Olfaction was measured in the Year 3 with the 12-item Cross-Cultural Smell Identification Test (23). We used previously calculated race- and sex-stratified tertiles of function (good, moderate, and poor) from Yaffe and colleagues (24) as the basis of defining olfactory impairment. Poor smell was defined as the lowest tertile of function. Lower extremity sensory nerve function was assessed in Year 4 study visit with two different tests. Vibration detection threshold (in μ m) was measured at the bottom of the big toe. Prior work in Health ABC has determined a cut point of more than 130 μ m to be clinically meaningful (25,26). Monofilament tested with a standard 10 g and light 1.4 g monofilament; impaired sensitivity defined as the inability to detect three of four touches with monofilament. We categorized sensory impairment based on impairment in the 10 g monofilament or vibration threshold limit. Audiometric assessments were performed in a sound-treated booth in Year 5 study visit. Participants were not allowed to use hearing aids. Pure tone average was calculated from audiometric thresholds at 0.5, 1, 2, and 4 kHz for the better hearing ear. Pure tone average greater than 40 dB hearing level was defined as moderate-to-severe hearing loss (8,27).

Dementia

Similar to prior Health ABC studies (8,24,28), dementia was defined as meeting one or more of the following criteria through study Year 15 (2011–2012): (a) hospitalization with dementia as a primary or secondary diagnosis, (b) documented use of dementia medication, or (c) clinically meaningful Modified Mini-Mental State Examination (3MS) (29) decline from Health ABC baseline (1.5 SD, race-stratified). Self-reported hospital admissions were collected every 6 months, and hospital records were reviewed for a primary or secondary dementia diagnosis; dementia medications were collected at annual visits. The 3MS was administered in Years 1 (1997–1998), 3 (1999–2000), 5 (2001–2002), 8 (2004–2005), 10 (2006–2007), and 11 (2007–2008). Date of diagnosis was defined as the first date at which the participant met at least one of the above criteria. Over follow-up, 336 participants met criteria for dementia; the majority of cases were based on hospitalizations either alone (44%) or in combination with other sources (32%). Of dementia cases, 10% were based on medications only, 12% on 3MS decline only, and 2% on both medications and 3MS decline.

Covariates

Sex, race, educational attainment, and study site were recorded in Year 1. Age at Year 5 was considered in this analysis. History of health conditions cumulative up to Year 5 was defined based on a combination of participant interview, medical record review, medications, and baseline laboratory values. Health conditions included hypertension, diabetes, cardiovascular disease (myocardial infarction, congestive heart failure, etc.), and cerebrovascular disease (stroke, transient ischemic attack). Depression was defined as 10 or higher on the Center for Epidemiologic Study Depression Scale short form (30). Body mass index at Year 5 was calculated as kg/m². Apolipoprotein $\epsilon 4$ allele status was defined as (1+ $\epsilon 4$ allele vs none) based on serum assay. Participants were also asked about health behaviors (smoking, alcohol consumption, and physical activity). Smoking status at Year 5 was categorized as never, current, or former. Alcohol consumption was assessed at Year 1 only; heavy

alcohol consumption (yes, no) was defined in this analysis as more than one drink per day. Minutes spent walking and briskly walking at Year 5 was calculated from a structured interview on daily physical activities.

Statistical Analyses

First, we examined the co-occurrence of sensory impairments. Next, using descriptive statistics we compared participant characteristics between those with no sensory impairment, single sensory impairment, and multisensory impairment (impairment in two or more senses).

Participants were followed from Year 5 (analytic baseline) until dementia diagnosis; those without dementia were censored at the last available date of contact. We used multivariable Cox proportional hazard models to assess the relationship between sensory impairment and time to dementia diagnosis. We assessed associations with the number of sensory impairments as the primary predictor. No sensory impairment was the reference group; we additionally tested for a difference between multiple impairments and a single impairment based on linear combinations of coefficients in the same model. We included two models with increasing adjustment for potential confounders; Model 1 included adjustment for demographics and Model 2 included adjustment for demographics plus comorbid conditions and health behaviors. Owing to concern that subtle cognitive impairments may affect sensory assessment, we ran a sensitivity analysis additionally adjusting for baseline cognition (Year 5 3MS score). We included interactions between primary predictors and race, sex, and APOE $\epsilon 4$ allele to test whether associations differed for subgroups. As olfaction may be a marker of neurodegeneration, for example preclinical Alzheimer's disease (31), we assessed associations of multisensory impairment based on hearing, vision, and touch adjusting for olfaction. We also assessed associations between individual sensory impairments and dementia risk because associations may differ by type of sensory impairment. In models for vision, we included additional adjustment for history of common causes of visual impairment as a sensitivity analysis. First, we examined individual sensory impairments in separate models, next we included each sensory impairment in one model simultaneously to assess whether each sensory impairment was associated with dementia independent of each other. All tests were two-sided with $\alpha = .05$. Analyses were conducted in R (version 3.4.1).

Results

Sensory impairment was common (Table 1). Almost 40% of participants ($n = 709$) had impairment in a single sense; 75% of the sample wore glasses during the vision testing and 13.1% reported daily use of hearing aids. Multisensory impairment was prevalent in 26% of participants ($n = 466$), and 6% of participants had impairment in three or four senses. Among those with multisensory impairment ($n = 466$), the most frequent combinations of impairments were vision + hearing, followed by smell + hearing and smell + vision (Figure 1). Pairwise combinations of hearing + touch, vision + touch, and vision + smell were more likely than expected by chance $\chi^2 p < .01$ (Supplementary Table 1). Compared to those with no sensory impairments, participants with multisensory impairment tended to be older and were more likely to be male, white, had comorbidities, and were less educated (Table 2).

Over follow-up, 336 participants (19%) developed dementia: 12% in those with zero sensory impairments, 19% in those with

Table 1. Distribution of Sensory Impairments

Sensory Impairment	
Vision	503 (27.8)
Poor visual acuity	140 (7.7)
Low contrast sensitivity	476 (26.3)
Smell	
Normal	905 (50.0)
Moderate	500 (27.6)
Poor	405 (22.4)
Touch	218 (12.0)
Monofilament 1.4 g	807 (44.6)
Monofilament 10 g	150 (8.3)
Unable to detect vibration	103 (5.7)
Hearing	
Normal	466 (25.7)
Mild	715 (39.5)
Moderate-to-severe	629 (34.8)
Number of impairments	
0	635 (35.1)
1	709 (39.2)
2	363 (20.1)
3	92 (5.1)
4	11 (<1)

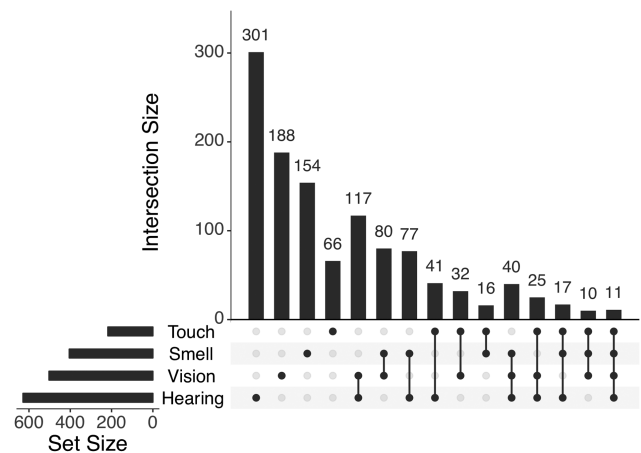


Figure 1. Overlap of sensory impairments by frequency. This figure shows the frequency of each combination of sensory impairments in decreasing order of frequency L-R, ordered in by number of co-occurring sensory impairments. Dots represent individual sensory impairments, with lines connected to represent co-occurring impairments. Impaired hearing, vision, and smell without other impairments were the most frequent, followed by pairwise combinations of vision + hearing, smell + vision, smell + hearing, hearing + touch, and the three-way combination of hearing + vision + smell.

one sensory impairment, and 28% in those with multisensory impairment. Increasing number of impairments was associated with risk of dementia in a graded fashion in unadjusted Kaplan-Meier estimates (Figure 2) and after adjustment for potential confounders (all $ps < .01$ for increased number of impairments vs none) (Table 3). In fully adjusted models, participants with three or four sensory impairments were 2.85 times more likely to develop dementia ($p < .001$) than those without any sensory impairments (Table 3) and 1.91 times more likely to develop dementia compared to those with one sensory impairment (95% CI: 1.31, 2.79; $p < .001$ calculated via linear combinations of coefficients). Additional adjustment for 3MS score at Year 5 slightly attenuated the magnitude of effects but

Table 2. Baseline Characteristics by Number of Sensory Impairment

Characteristics, <i>n</i> (%) or mean (<i>SD</i>)	No Sensory Impairment, <i>N</i> = 635	Single Impairment, <i>N</i> = 709	Multiple Impairment, <i>N</i> = 466
Age (y), mean (<i>SD</i>)	76.7 (2.6)	77.5 (2.7)	78.3 (3.1)
Female	385 (60.6)	358 (50.5)	195 (41.8)
Black	242 (38.1)	221 (31.2)	167 (35.8)
Completed high school	536 (84.4)	568 (80.1)	334 (71.7)
Body mass index, mean (<i>SD</i>)	27.4 (4.9)	27.2 (4.5)	27.2 (4.7)
Hypertension	524 (82.5)	582 (82.1)	383 (82.2)
Cardiovascular disease	106 (16.7)	161 (22.7)	97 (20.8)
Stroke/TIA	92 (14.5)	112 (15.8)	85 (18.2)
Diabetes	98 (15.4)	156 (22.0)	126 (27.0)
Depression	133 (20.9)	151 (21.3)	129 (27.7)
APOE-ε4 [†]	183 (30.6)	172 (25.6)	109 (24.9)
Current smoker	38 (6.0)	37 (5.2)	33 (7.1)
Alcohol use (>1 drink/d)	50 (7.9)	59 (8.3)	35 (7.5)
90 min of brisk walking/wk	63 (9.9)	61 (8.6)	33 (7.1)
0 min of walking/wk	272 (42.8)	313 (44.1)	245 (52.6)

Notes: APOE = apolipoprotein E; TIA = transient ischemic attack.
[†]Missing data: APOE = 102 (5.6%).

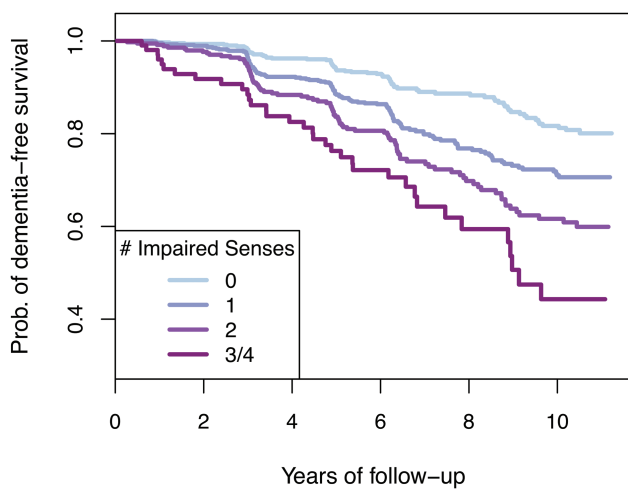


Figure 2. Kaplan-Meier estimate of risk of dementia by number of sensory impairments (vision, smell, hearing, and touch).

Table 3. Association Between Risk of Dementia and Total Number of Sensory Impairments

Number of Sensory Impairments	Demographic Adjusted [†] HR (95% CI)	Multivariable [‡] HR (95% CI)
0	1.00 (reference)	1.00 (reference)
1	1.58 (1.19, 2.11)	1.49 (1.12, 1.98)
2	2.13 (1.56, 2.90)	1.91 (1.39, 2.63)
3 or 4	3.18 (2.11, 4.81)	2.85 (1.88, 4.30)

Notes: [†]Model adjusted for age, race, sex, and education.
[‡]Demographic adjusted model + hypertension, diabetes, cardiovascular disease, cerebrovascular disease, smoking status, alcohol use, and physical activity.

did not change interpretations (all *ps* < .01 for increasing number of impairments vs none). Interactions between increasing number of sensory impairments and race, sex, and APOE ε4 allele status were not significant (all *ps* > .5). Sample sizes were small for race- and

sex-stratified analyses; estimates were less precise but similar by race and sex to the overall findings for white men, black men, and black women (Table 4). In white women, there was no evidence for a graded increase risk of multisensory impairment. Compared to black and white men and black women, white women were more likely to have completed high school and less likely to have diabetes or a body mass index more than 30 kg/m² (all χ^2 *ps* < .001).

Smell, touch, and hearing were individually associated with risk of dementia after adjustment for demographics, health conditions, and lifestyle factors (all *ps* < .05; Table 5). Risk of dementia was elevated for poor visual acuity and low contrast sensitivity in models adjusted for demographics only, but confidence intervals were wide (all *ps* > .05). Estimates were slightly attenuated after additional adjustment for cataracts, age-related macular degeneration, glaucoma, and retinopathy but interpretations did not change. With simultaneous inclusion of vision, hearing, smell, and touch in one model, poor smell remained significantly associated with risk of dementia (hazard ratio = 2.16; 95% CI: 1.72, 2.70; *p* < .001) and touch was borderline associated with risk of dementia (hazard ratio = 1.34; 95% CI: 0.99, 1.80; *p* = .06). In a sensitivity analysis that adjusted for poor smell, the association between multiple impairments in hearing, vision, or touch and dementia was slightly attenuated but remained significant (hazard ratio = 1.67; 95% CI: 1.03, 2.72; *p* = .04).

Discussion

We studied multisensory impairment and risk of dementia among black and white older adults. With increasing number of impairments, the risk of dementia increased in a dose-response manner. In fully adjusted models, the risk of developing dementia associated with having 3 or 4 sensory impairments was almost 3 times higher than having no sensory impairments and almost 2 times higher than having a single sensory impairment. Individually, most measures of sensory impairment were associated with slightly increased risk of dementia (smell, hearing, and touch). These findings were robust to adjustment for multiple potential confounders and in sensitivity analyses. Race- and sex-stratified estimates were similar in all but white women in whom a strong association for increasing impairments was not present. Additional research is needed to ensure this

Table 4. Association Between Risk of Dementia and Total Number of Sensory Impairments Stratified by Race and Sex

Number of Sensory Impairments	Black Women (N = 373)		White Women (N = 565)		Black Men (N = 257)		White Men (N = 615)	
	n	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)
0	160	1.00 (reference)	225	1.00 (reference)	82	1.00 (reference)	168	1.00 (reference)
1	128	1.61 (0.90, 2.89)	230	1.41 (0.87, 2.28)	93	1.25 (0.58, 2.72)	258	1.66 (0.92, 3.01)
2	72	1.82 (0.93, 3.56)	90	1.35 (0.71, 2.55)	57	2.12 (0.99, 4.54)	144	2.46 (1.29, 4.66)
3 or 4	13	3.36 (1.38, 8.19)	20	0.87 (0.24, 3.11)	25	3.81 (1.34, 10.88)	45	3.96 (1.95, 8.05)

Note: Model adjusted for age, race, sex, education, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, smoking status, alcohol use, and physical activity.

Table 5. Association Between Risk of Dementia and Individual Sensory Impairments

Sensory Impairments	Demographic Adjusted [†] HR (95% CI)	Multivariable [‡] HR (95% CI)
Vision (N = 2,008)		
Visual acuity	1.33 (0.93, 1.88)	1.26 (0.90, 1.77)
Contrast sensitivity	1.22 (0.97, 1.53)	1.11 (0.88, 1.38)
Smell (N = 2,017)	2.10 (1.71, 2.60)	1.78 (1.42, 2.23)
Touch		
Vibration threshold (N = 1,954)	1.65 (1.14, 2.38)	1.56 (1.08, 2.26)
10g monofilament (N = 1,987)	1.46 (1.05, 2.02)	1.39 (1.01, 1.93)
Hearing (N = 2,027)	1.24 (1.004, 1.54)	1.25 (1.01, 1.55)

Notes: [†]Each impairment is a predictor in separate models adjusted for age, race, sex, and education (vision acuity and contrast sensitivity additionally adjusted for use of corrective lenses in testing).

[‡]Demographic adjusted models + hypertension, diabetes, cardiovascular disease, cerebrovascular disease, smoking status, alcohol use, and physical activity.

finding is not due to a small sample size. Together our findings suggest that individuals with multisensory impairment are a high-risk population that could be targeted prior to dementia onset for intervention.

Impairment in multiple sensory domains is an important predictor of dementia in older adults. This work is an important extension from prior work in Health ABC and other populations in which impairment in hearing, vision, and olfaction are individually associated with risk of dementia (5,6,8,10,24,32), and may have independent effects (7,9). Unlike prior studies on contrast sensitivity (7,9,10), we did not find significant associations between visual impairments and cognition; this may be due to a smaller sample size, use of a binary variable, or the high visual function in the sample. Associations with dementia were strongest for smell but also moderate for hearing and for touch. Few studies have reported a link between impaired touch (operationalized by peripheral neuropathy measures) and cognition independent of diabetes. Impaired peripheral sensation affects up to 70% of older adults (1) and is associated with poor mobility even in those without diabetic neuropathy (25,26).

Few studies have quantified the effects of multisensory impairment on cognitive impairment. Combined hearing and visual impairment has been associated with added risk compared to one impairment in some (4,33) but not all studies (34). Another study found impairments among five senses (operationalized as global sensory impairment) predicted lower cognitive function but did not test for graded effects (17). Assessment of multiple types of sensory

function may be a valuable tool for identifying older adults at high risk of poor health outcomes including cognitive decline (35). Future research should examine whether diagnostic and prognostic predictions for patients are improved by including multisensory assessments and whether interventions to prevent dementia could be targeted to those with multisensory impairment.

The link between sensory and cognitive function is challenging to tease apart. We treated sensory impairments additively to look at the overall association of multisensory impairments and dementia. The mechanisms underlying these associations and implications for clinical intervention may be shared or may differ by each type of sensory function. Effects were strongest with the addition of olfactory impairment, which may indicate underlying neurodegeneration, such as preclinical alzheimer's disease (31). However, even with control for olfactory impairment, increased number of impairments in hearing, vision, and touch remained a significant predictor of dementia. A combination of general aging processes, inflammation, as well as subclinical cardiovascular or metabolic disease may also explain the link between multiple sensory impairments and dementia (1,11,16,25,36,37). Increased impairments, particularly in hearing and vision, may also lead to social isolation, depression, worse physical activity, and functional limitations which may, in turn, lead to accelerated cognitive decline (15). In a study among nursing home patients, the association between dual sensory impairment of vision and hearing loss and cognitive decline was present only in those with low social engagement (33). It is also possible that those with visual or hearing impairments are more prone to measurement error in testing. Sensory function tests involve cognitive processing and decision making, and cognitive function tests involve auditory and visual cues, which increases cognitive load in testing (34,38). Additional studies are necessary to determine the biological pathways underlying the link between each type of sensory impairment and dementia. However, the strong associations found in our study suggest multisensory impairment does merely represent normal aging.

We recognize several important caveats and limitations in this study. Sensory measures were only collected once and not all in the same study year, this could lead to some misclassification particular for the multisensory measure. Sensory function gradually declines with age, on average (16), but some impairments can be corrected (eg, new glasses, cataract surgery) (39). As such misclassification would likely occur independent of future dementia risk, our findings may actually be biased toward the null, or more conservative than the true association. Sensory impairments were dichotomized and summed for simplicity; in general, those mild impairments were lumped together with no impairments. Future work may find larger and more graded effects by incorporating both severity and number of impairments into a multisensory measure. Our dementia variable is not a clinical diagnosis but based on an algorithm that may have

missed some individuals with dementia or included participants with mild cognitive impairment. This misclassification would likely further attenuate associations. Race- and sex-stratified subgroups were small and there was limited power to detect relationships. Finally, participants were highly selected to be healthy at baseline; this indicates our findings are especially robust but may not be generalizable to the general population.

This study also has appreciable strengths including a large biracial cohort of older adults followed for over 10 years. We used a definition of all-cause dementia that was based on multiple components and sources. We used multiple measures of sensory function, including touch, which has not been incorporated into many studies of cognition. We also assessed the combined effects of multiple sensory impairments on dementia risk as well as testing associations with individual sensory impairments.

Multisensory impairment was strongly associated with increased risk of dementia in this cohort of older black and white older adults. This study highlights the high prevalence of comorbid impairments in sensory function and a strong association with subsequent risk of dementia. Associations remained after accounting for comorbid health conditions as well as adjusting for impaired smell as a sign of preclinical alzheimer's disease. Additional studies will be needed to determine the exact nature of this relationship and whether this risk may be modified by treatments that improve sensory function such as the use of hearing aids or visual corrections. Assessment of sensory function in multiple domains may help identify patients at high risk of developing dementia.

Supplementary Material

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

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Conflict of Interest

Frank R. Lin is a consultant to Amplifon, Cochlear, and Boehringer Ingelheim. Allison R. Kaup is a scientific advisory consultant for Squint Metrics. All other authors have no conflicts.

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