Making Sense of Brain Aging: Hearing and Visual Impairments, Ophthalmic Conditions, and Risk of Dementia in Older Adults

Phillip H. Hwang

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Reading Committee:

Annette L. Fitzpatrick, Chair

W.T. Longstreth, Jr.

Stephen M. Thielke

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Abstract

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Phillip H. Hwang

Chair of the Supervisory Committee:
Annette L. Fitzpatrick, PhD, Research Professor
Family Medicine, Epidemiology, and Global Health

Background: Hearing and vision play an important role in physical, mental, and functional health. Less is known about the impact of deficits in hearing and vision, including dual sensory impairment (DSI), and causes of these sensory impairments on cognitive function. Objectives of this study were to examine risk of dementia associated with: (1) hearing and visual impairments in late-life; and (2) common ophthalmic conditions in older adults, such as cataracts, age-related macular degeneration (AMD), diabetic retinopathy (DR), and glaucoma.

Methods: Participants from the Ginkgo Evaluation of Memory (GEM) Study and the Cardiovascular Health Study (CHS) who were dementia-free at baseline were included in the analyses. Information on hearing and visual impairments were based on self-report at baseline in the GEM Study and CHS. Additionally, in CHS, data on hearing and vision were collected at multiple follow-up visits. Medical histories collected by CHS and ICD-9 diagnostic codes from Medicare Part B claims data were used to ascertain diagnoses of specific ophthalmic conditions.

Incident dementia, including major subtypes of Alzheimer's disease (AD) and vascular dementia (VaD), was adjudicated by a consensus committee using standardized criteria. Multivariable Cox models were used to estimate risk of dementia, presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Greater number of sensory impairments was associated with increased risk of dementia in a graded fashion in both the GEM Study (P = 0.002) and CHS (P <0.001). DSI at baseline was associated with increased risk for all-cause dementia (HR = 1.86; 95% CI = 1.25 – 2.76) and AD (HR = 2.12; 95% CI = 1.34 – 3.36) in the GEM Study. Time-varying DSI was also associated with increased risk for all-cause dementia (HR = 2.60; 95% CI = 1.66 – 4.06) and AD (HR = 3.67; 95% CI = 2.04 – 6.60) in CHS. DSI severity at baseline in the GEM Study was associated with risk for all-cause dementia in a dose-dependent fashion (P = 0.02). Longer duration of DSI was associated with increased risk for all-cause dementia in CHS (P = 0.02). In CHS, increased risk for AD was associated with AMD (HR = 1.87; 95% CI = 1.13 – 3.09) and cataracts (HR = 1.34; 95% CI = 1.01 – 1.80). Increased risk for VaD was associated with DR (HR = 2.63; 95% CI = 1.10 – 6.27) and cataracts (HR = 1.41; 95% CI = 1.02 – 1.95).

Conclusions: Older adults with hearing and visual impairments are at elevated risk of developing dementia. Differential associations between cataracts, AMD, DR, and incident dementia may reflect heterogeneous underlying neurodegenerative and vascular pathways shared between the eye and brain. Evaluation of hearing and vision, including common ophthalmic conditions associated with vision loss, may represent important areas for interventions in older adults to promote healthy cognitive aging.

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DEDICATION

To my wife and family for their unconditional love, support, and encouragement, which sustained me through some of my most challenging days. I have also been uplifted many times by the newest addition to our family, Garlic, who reminds me to find joy in the simple and present.

I say to the Lord, "You are my Lord; I have no good apart from you." (Psalm 16:2)

Chapter 1. INTRODUCTION

Hearing and visual impairments constitute some of the most common health problems in older adults. Hearing loss affects at least 28 million adults in the US [1], with approximately 33% of adults aged 61 to 70 years and more than 80% of those aged 85 years and above affected by hearing loss [2,3]. It is the third most common chronic health problem in older adults following hypertension and arthritis [4]. Vision loss affects around 37 million US adults older than 50 years, with about 25% of those older than 80 years affected by vision loss [5]. The conditions that cause most cases of vision loss in older adults are age-related macular degeneration (AMD), glaucoma, ocular complications of diabetes mellitus, and age-related cataracts [6]. Individuals with concurrent hearing and visual impairments, known as dual sensory impairment (DSI), comprise a relatively smaller subgroup, with about 22% of adults 65 years and older estimated to have DSI [7]. Given that the prevalence of these sensory impairments increases with age, the impact of hearing and vision loss on society will continue to grow as the number of older individuals increases [5,8,9].

Consequences of hearing and visual impairments in older adults include negative effects on physical and mental health, as well as a functional and overall well-being. Hearing loss impacts communication and functional ability, and is strongly associated with decreased quality of life and depression [8,10]. Vision loss in older adults is associated with increased risk of falls, loss of independence, depression, and increased all-cause mortality [11-14]. Compared to those with single sensory loss in hearing or vision, or intact sensory acuity, older adults with DSI have greater disparities in health and social outcomes, such as functional disability, communication, social activity, depressive symptoms, hospitalizations, and mortality [15,16]. In addition to these effects of hearing and visual impairments, deficits in hearing and vision are individually associated with cognitive decline or increased risk of cognitive impairment and dementia in older adults [17-20]. Dementia, like sensory impairment, is strongly related to age. Consequently, with a rapidly aging population, as well as lack of effective treatments that can stop or slow the disease process, the burden of dementia is expected to exert an enormous impact on patients, families and caregivers, health care systems, and economic costs [21].

The associations between hearing and vision, ophthalmic conditions, and cognition may be explained by different hypothesized mechanisms, which are depicted as a conceptual model adapted from Whitson et al. [22] below in **Figure 1.1**.

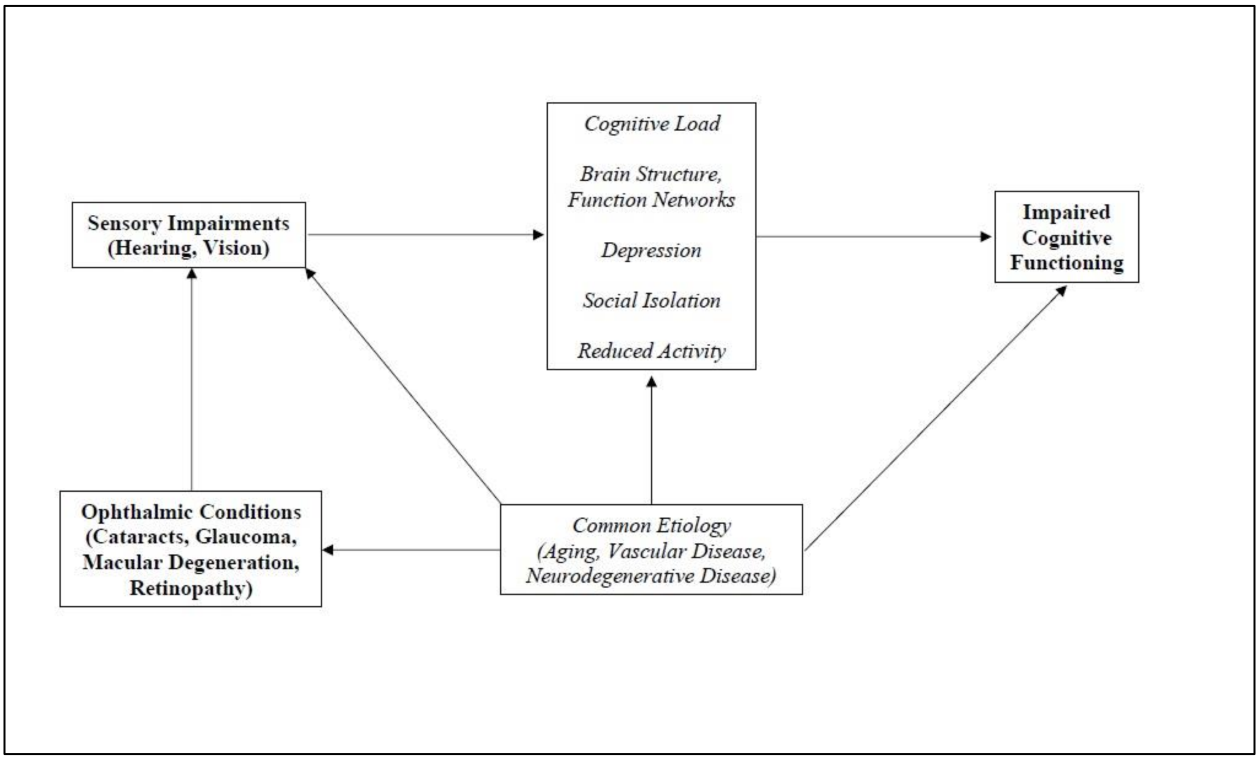

Figure 1.1. Conceptual model of mechanisms and pathways between hearing, vision (eye), and cognitive function.

First, hearing and visual impairments, as well as common ophthalmic conditions in older adults, may be causally related to cognitive impairment. By increasing cognitive load, these conditions might limit the neural resources needed for optimal performance of cognitive tasks. Loss of sensory input may also directly alter brain structure and function, as well as lead to depression, social isolation, and lack of physical activity, which could cause cognitive impairment [22]. Second, a common pathological process, such as vascular disease, may be responsible for sensory loss, ophthalmic conditions, and cognitive impairment in older adults. For example, β-amyloid, a pathological hallmark of Alzheimer's disease (AD), has been found to be present in the ocular lens and retina [23,24], and its presence may be a biomarker for AD, which is the most common cause of dementia [21]. With evidence providing suggestive clues as to how hearing and vision are related to cognition, additional studies are still needed to empirically test the proposed theories on possible pathways between sensory impairment and cognitive dysfunction.

As these relationships are likely to be multifactorial, further research is necessary to clarify the roles of sensory impairments and ophthalmic conditions on cognitive function. A methodologic challenge in disentangling these different explanations is that hearing and vision rely on cognitive processes, and cognitive testing involves visual or auditory tasks [22], so measuring cognitive ability may be less accurate in the presence of hearing or vision problems. Other important areas of research include examining the impact of multiple sensory impairment, such as DSI, on risk of dementia, which is lacking in the literature. Several studies have already found an association between DSI and cognitive decline and impairment [25-29]. Additional studies on the associations between ophthalmic conditions, such as cataracts, glaucoma, diabetic retinopathy (DR), and AMD, and incident dementia are needed as well since much of what is known so far about the connection between the eye and brain comes from animal models or small studies in humans [30,31].

This dissertation project addressed some of these gaps in knowledge by conceptually shifting from a focus on individual or single sensory impairment towards a more complete view of sensory impairment burden in older adults. Leveraging rich, well-established data sources focused on older adults that spanned several years of follow-up, along with collected baseline and repeated measures of sensory impairments and rigorous ascertainment of dementia, including its major subtypes of AD and vascular dementia, facilitated a strong methodologic approach to the project. Use of advanced statistical methods, such as marginal structural models with inverse probability weighting, strengthened the analytic approach and validity of model-based estimates of dementia risk by addressing potential bias arising from complex, longitudinal data. Finally, integration of multiple disciplines, such as neuroscience, geriatrics, neurology, psychiatry, ophthalmology, and speech and hearing sciences, supported this scientific investigation in a systematic manner that was guided by a more holistic view of the relationships between hearing and visual impairments, ophthalmic conditions, and dementia.

The following chapters (2, 3, and 4) present the manuscripts for studies, which have either been published or are currently under review for publication. Chapter 2 examines the association between DSI, which was measured only once at study baseline, and risk of dementia from the Ginkgo Evaluation of Memory Study. Chapter 3 extends the findings from Chapter 2 by examining longitudinal measures of hearing and visual impairment in relation to dementia risk within the Cardiovascular Health Study (CHS). Chapter 4 focuses on the major causes of vision loss in older adults and examines associations between specific ophthalmic conditions, including cataracts, glaucoma, AMD, and DR, and risk of dementia in CHS. Finally, Chapter 5 concludes with an overview of the findings from the preceding chapters and presents several remaining unanswered questions that can be addressed in future studies. Together, these studies will help to advance knowledge of the role that sensory function plays on the brain, along with the importance of evaluating hearing and vision in older adults to aid in the prevention of dementia and promotion of healthy cognitive aging.

Chapter 2. ASSOCIATION BETWEEN BASELINE DUAL SENSORY IMPAIRMENT AND RISK OF DEMENTIA IN THE GEM STUDY

2.1 Prior Publication

Chapter 2 has been published in Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring [32], and involves collaboration with the following co-authors: W.T. Longstreth, Jr., Willa D. Brenowitz, Stephen M. Thielke, Oscar L. Lopez, Courtney E. Francis, Steven T. DeKosky, and Annette L. Fitzpatrick. For the purposes of this dissertation, Phillip Hwang was solely responsible for the conception and design of the study, analysis of the data, and for the writing of all sections of the manuscript. The published journal article can be found online at: https://alz-journals.onlinelibrary.wiley.com/doi/epdf/10.1002/dad2.12054

2.2 Background

Hearing and visual impairments are common in older adults, with an estimated 33% of individuals aged 70 years and older affected by hearing loss and 18% affected by vision impairment [33,34]. As the incidence and prevalence of these sensory impairments increase with age, hearing and vision loss will affect a growing proportion of the population [22,34]. Sensory impairment is associated with increased risk of mortality and functional difficulties [16,35,36]. Several prospective studies also found that hearing and visual impairments in older adults independently increase risk of cognitive impairment and dementia [17-19,37,38]. Causal effects have been hypothesized due to sensory loss precipitating social isolation, depression, and reduced physical activity [39,40]. Alternatively, sensory and cognitive impairment may share similar disease processes, such as cerebrovascular disease [41-43] or neurodegeneration [44]. While most prior studies have focused on impairments in hearing and vision individually, the impact of having combined hearing and visual impairment, or dual sensory impairment (DSI), on dementia risk is unclear. In the US, DSI affects up to 15% of adults, with the highest prevalence among adults age 80 years and older [15,45]. Studies examining both hearing and vision found that an increasing number of impairments may have a greater impact on health outcomes and increased mortality than a single sensory deficit [36,46]. Compared to the presence of only one impairment, DSI may also increase the risk of cognitive impairment [46]. Other studies, however, found no added risk of cognitive impairment [47] and suggested that sensory impairment in more than one domain may reflect a shared common aging process [48,49]. More recent work showed that a greater number of sensory impairments was associated with increasing risk of dementia in a graded fashion, which included a combination of hearing, smell, touch, and vision assessments [50]. Additional research is needed to quantify the effects of concurrent hearing and visual impairment on dementia risk. Few studies have characterized the impact of DSI specifically on dementia risk using a prospective study design with rigorous ascertainment of dementia and its major subtypes: Alzheimer's disease (AD) and vascular dementia (VaD).

In this study, we investigated associations between hearing and visual impairments in late life with incident dementia among participants of the Ginkgo Evaluation of Memory (GEM) Study. It included self-reported hearing and vision at enrollment plus the rigorous evaluation of dementia and its subtypes during follow-up in this cohort of older adults who were either cognitively normal or met criteria for mild cognitive impairment (MCI). We hypothesized that DSI would be associated with an increased risk for dementia as compared to no or a single sensory impairment.

2.3 METHODS

The GEM Study was originally designed as a double-blind randomized controlled trial to determine the efficacy of *Ginkgo biloba* (*G. biloba*) in the prevention of dementia among older adults [51]. Although results of the GEM Study were negative, data serve as a useful platform to address other scientific questions in older adults related to cognition and dementia. Institutional Review Boards of all universities involved in the study approved the study protocol, as did the National Institutes of Health. All participants and their proxies signed approved informed consent forms.

2.3.1 *Study Participants*

Volunteers aged 75 years and older were recruited from September 2000 to June 2002 using voter registration and other purchased mailing lists of four US communities with academic medical centers. Until the end of the study in 2008, 3,069 participants were assessed every six months for incident dementia. Although individuals with prevalent dementia were excluded from participation, participants with MCI were not. Participants also had to have adequate hearing and vision, based on the judgment of clinical study staff, in order to be included in the study [52]. Additional information on exclusion criteria and criteria for classification of MCI at baseline in the GEM Study have been described elsewhere [51,52].

2.3.2 *Data Collection*

Data collected at baseline included vital signs, medication use, detailed medical history, physical function assessment, physical and neurologic examinations, and apolipoprotein E (ApoE) genotype. Symptom and health habit questionnaires included self-reported questions on cardiac, neurological, and gastrointestinal symptoms, as well as questions on smoking, alcohol use, and exercise. ApoE ε4 carrier status was assayed from stored blood. Dropout and loss to follow-up rates were low at 6.3% [51].

2.3.3 *Dementia Ascertainment*

Cognitive function was evaluated by administering at baseline the Clinical Dementia Rating scale [53], Modified Mini-Mental State Exam (3MSE) [54], and the cognitive subscale of the Alzheimer's Disease Assessment Scale [55]. Participants also completed a neuropsychological battery of tests at baseline to determine whether they were free of dementia and to establish baseline cognitive scores. Participants with worsening scores on the neuropsychological battery due to poor hearing or vision continued follow-up visits until there was evidence of decline on a broad range of tests not limited to those involving hearing or vision [52]. Incident dementia was determined in a standard fashion, as has been detailed previously [51]. This included taking into consideration the effects of hearing or visual problems at the time of dementia classification by the adjudication committee, which had a narrative from the examiner in each dementia case. All participants who were adjudicated as developing incident dementia, based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4^{th} edition [56], were assigned to one of the following specific categories: (1) Alzheimer dementia only; (2) Alzheimer dementia and vascular dementia; (3) vascular dementia only; or (4) dementia, other etiology (dementia with Lewy bodies, Creutzfeldt-Jakob disease, etc.). Designation of specific dementia subtypes were based on the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association [57], National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences [58,59], and Alzheimer's Disease Diagnostic and Treatment Centers [60] diagnostic criteria.

2.3.4 *Hearing and Visual Impairment*

Hearing and vision were assessed through self-report at baseline of the GEM Study. For hearing, participants were asked: (1) Can you hear well enough (with or without) a hearing aid to listen to the radio; (2) Can you hear well enough (with or without) a hearing aid to use the telephone; and (3) Can you hear well enough (with or without) a hearing aid to carry on a conversation in a crowded room? For vision, participants were asked: (1) Can you see well enough (with or without) glasses to drive; (2) Can you see well enough (with or without) glasses to watch TV; (3) Can you see well enough (with or without) glasses to read the newspaper; and (4) Can you see well enough (with or without) glasses to recognize someone across the room? Hearing impairment was defined as a negative response to one or more of the three hearing questions. Visual impairment was defined as a negative response to one or more of the four vision questions. Participants classified with hearing impairment and visual impairment were defined as having DSI.

2.3.5 *Statistical Analysis*

The primary analysis compared the time to all-cause dementia and number of sensory impairments (0, 1, or 2) at baseline. Time to dementia was calculated as days from baseline to dementia onset, death, or the end of GEM Study follow-up. The first visit was in September

2000 and the final visit was completed in April 2008. Participants were censored at the date of last contact, including end of the study, or date of death. The date of dementia onset was estimated as the date midway between the last clinic examination at which the participant was not demented and the examination at which the dementia diagnosis was made.

Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs). In the analysis, the time axis was participant age at randomization in the GEM Study to control more finely for the effect of age on dementia risk. Models were adjusted for baseline covariates, including sex, age, race, education, income, body mass index, smoking status, alcohol intake, physical activity, hypertension, diabetes, history of cardiovascular disease and cerebrovascular disease, and ApoE ε4 allele status. Treatment status (*G. biloba* vs. placebo) and clinic site were included as additional potential confounders. Separate models were developed for all-cause dementia, AD only, and VaD (with or without AD). We included interactions between the number of sensory impairments and age, sex, and ApoE genotype to test whether associations with all-cause dementia differed in subgroups. We also stratified participants with MCI and without MCI (cognitively normal) at baseline to assess the possibility of reverse causation attributable to preclinical dementia. P <0.05 was considered statistically significant, and all tests were two-sided. Analyses were conducted using Stata version 14 (StataCorp, College Station, Texas). Venn/Euler diagrams were created using eulerAPE, which accurately illustrate the overlap of hearing and visual impairments [61].

To evaluate whether a dose-response relationship existed with risk for all-cause dementia, we constructed a summary score of impairments as a best approximation for DSI severity. As a continuous measure, a score from 1-6 was used to define severity. A score of 1 represented impairment in a single question for both vision and hearing each. A score of 2 represented impairments in two questions for hearing and in a single question for vision, or impairments in a single question for hearing and in two questions for vision. A score of 3 represented impairments in all three questions for hearing and in a single question for vision, impairments in two questions for hearing and in two questions for vision, or impairments in a single question for hearing and in three questions for vision. A score of 4 represented impairments in a single question for hearing and in all four questions for vision, impairments in two questions for hearing and in three questions for vision, impairments in all three questions for hearing and in two questions for vision. A score of 5 represented impairments in all three questions for hearing and in three questions for vision, or impairments in two questions for hearing and in all four questions for vision. A score of 6 represented impairment in all questions for vision and hearing. As a categorical measure, scores were classified into "high," "intermediate," and "low" groups. Based on the summary score scale, "high" severity was defined as having a score of 5-6; "intermediate" severity was defined as having a score of 3-4; "low" severity was defined as having a score of 1-2. No DSI was the reference group.

In addition, we assessed associations between individual sensory impairments and risk of dementia, including AD and VaD, because associations may differ between types of sensory impairment (vision versus hearing). We first examined individual sensory impairments in separate models. Then, we included each sensory impairment in one model simultaneously to assess whether each sensory impairment was associated with dementia independently of each other.

Sensitivity analyses included the following: 1) restricting to diagnosis of probable AD only for models using (possible and probable) AD as the outcome; and 2) treating death as a competing risk, as well as non-AD for analyses with AD as the outcome, and non-VaD for analyses with VaD as the outcome. To evaluate potential bias due to missing covariate and predictor data, we used multiple imputation using chained equations to create 20 imputed datasets [62], and compared results from the imputed data to the primary complete case analysis.

2.4 RESULTS

A total of 2,051 participants without missing data constituted the analytic study sample. Most participants did not have self-reported hearing or visual impairment at baseline, while 22.8% had hearing or visual impairment and 5.1% had DSI with both hearing and visual impairment (**Figure 2.1**).

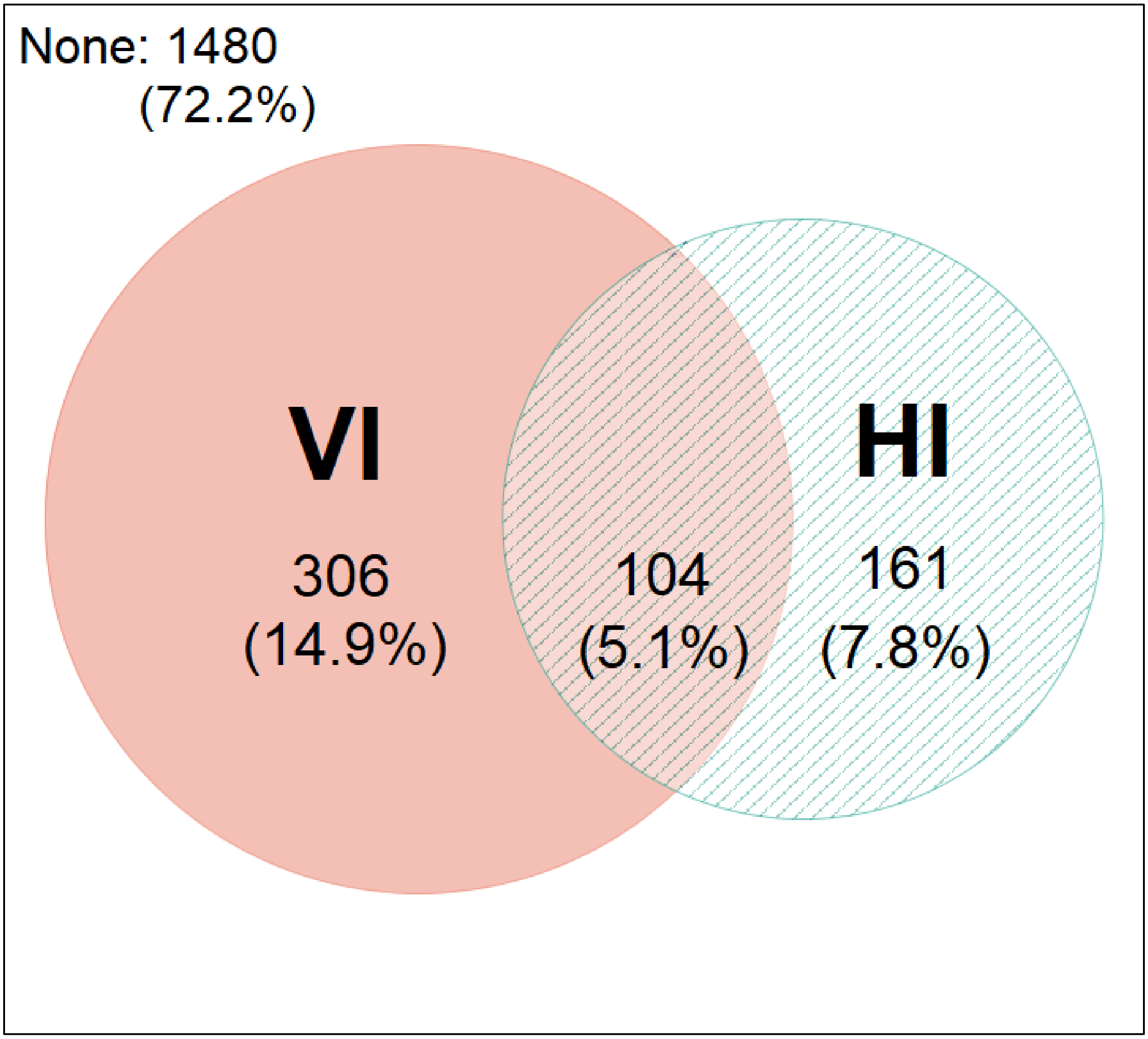

Figure 1.1. Conceptual model of mechanisms and pathways between hearing, vision (eye), and cognitive function.

Compared to participants without sensory impairment, participants with DSI tended to be older, were more likely to be male and have more co-morbidities, smoked previously, and consume more alcohol (**Table 2.1**).

Table 2.1. Baseline characteristics of study participants from the Ginkgo Evaluation of Memory (GEM) Study (2000-2008) by number of sensory impairments

Characteristic, n (%) or mean (SD)	**No sensory impairment (n = 1,480)**	**Single sensory impairment (n = 467)**	**Dual sensory impairment (n = 104)**
Age (years)*, mean (SD)	78.4 (3.1)	78.5 (3.2)	79.1 (3.5)
Sex			
Female	653 (44.1)	218 (46.7)	34 (32.7)
Male	827 (55.9)	249 (53.3)	70 (67.3)
Race			
White	1,438 (97.2)	451 (96.6)	100 (96.1)
Non-white	42 (2.8)	16 (3.4)	4 (3.9)
Education (years), mean (SD)	14.6 (3.1)	14.3 (3.4)	14.0 (3.2)
Body mass index†, mean (SD)	27.1 (4.2)	27.3 (4.2)	27.1 (4.1)
Cardiovascular disease‡	317 (21.5)	105 (22.5)	26 (25.0)
Cerebrovascular disease§	112 (7.6)	48 (9.2)	11 (10.6)
Diabetes	134 (9.1)	43 (9.2)	13 (12.5)
Hypertension¶	804 (54.3)	241 (51.2)	58 (55.8)
Smoking status			
Current smoker	71 (4.8)	16 (3.4)	5 (4.8)
Former smoker	813 (54.9)	276 (59.1)	61 (58.7)
Never smoker	596 (40.3)	175 (37.5)	38 (36.5)
Drinks per week, mean (SD)	3.7 (6.7)	3.5 (6.6)	5.0 (8.0)
Blocks/miles walked per week, mean (SD)	7.3 (8.6)	7.8 (10.0)	6.9 (7.9)
3MSE score#, mean (SD)	93.6 (4.6)	93.0 (4.7)	91.9 (4.7)
ApoE ε4**			
≥1 ε4 allele	356 (24.1)	109 (23.3)	23 (22.1)
No ε4 allele	1,124 (75.9)	358 (76.7)	81 (77.9)
Treatment status			
G. biloba	747 (50.5)	233 (49.9)	53 (51.0)
Placebo	733 (49.5)	234 (50.1)	51 (49.0)

*Age = Age at randomization; †Body mass index = kilograms/meters^2; ‡Cardiovascular disease = Self-reported history of the following conditions (heart attack, angina, heart failure, coronary bypass surgery, balloon angioplasty); §Cerebrovascular disease = Self-reported history of stroke, or transient ischemic attack/small stroke; ¶Hypertension = Blood pressure greater than 140/90, or use of anti-hypertensives; #3MSE score = Modified Mini-Mental State Examination; **ApoE ε4 = Apolipoprotein E ε4 allele

Most missing data came from absent ApoE genotype information (20.1%), which was due to lack of informed consent or technical problems with the blood samples from the clinical laboratory.

2.4.1 *Associations with Dementia*

Over 11,392 person-years of follow-up, 321 participants (15.6%) developed all-cause dementia: 14.3% in those with no sensory impairments, 16.9% in those with one sensory impairment, and 28.8% in those with DSI. Increasing number of sensory impairments was associated with risk of all-cause dementia in a graded fashion based on crude Kaplan-Meier estimates (**Figure 2.2**).

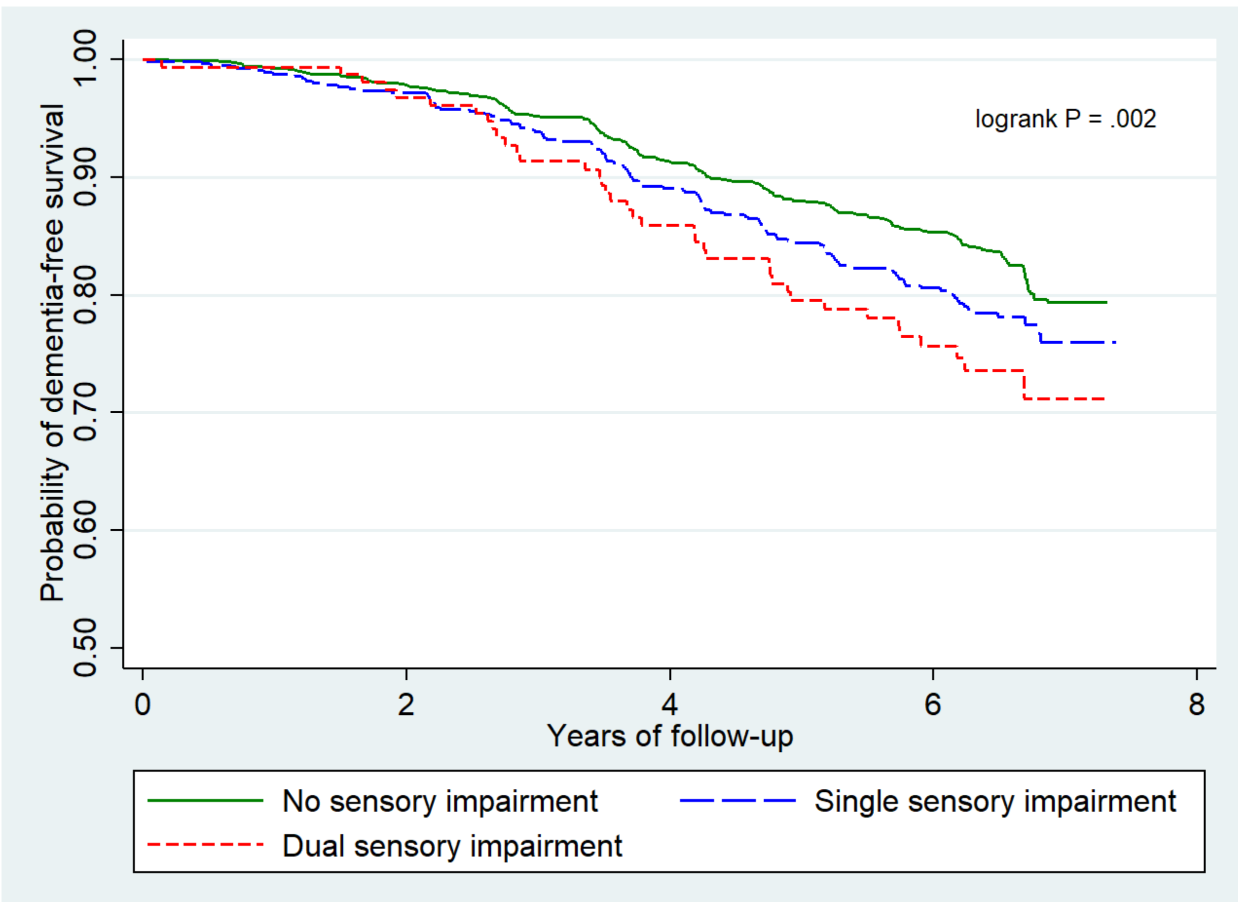

Figure 1.1. Conceptual model of mechanisms and pathways between hearing, vision (eye), and cognitive function.

In fully adjusted models, participants with DSI were 1.86 times more likely to develop all-cause dementia (95% CI = 1.25 – 2.76; *P* = 0.002) than those without any sensory impairments, while participants with DSI were 2.12 times more likely to develop AD (95% CI = 1.34 – 3.36; *P* = 0.001) than those without any sensory impairments (**Table 2.2**). Trends across the three levels were also significant for all-cause dementia and AD (**Table 2.2**). Significant associations were not present for single sensory impairment as the predictor or with VaD as the outcome.

Table 2.2. Associations between total number of sensory impairments at baseline and risk of incident all-cause dementia, Alzheimer's disease, and vascular dementia

	All-cause dementia (n = 321)		**Alzheimer's disease (n = 220)**		**Vascular dementia (n = 86)**	
Number of Sensory Impairments	**Hazard Ratio (95% CI)***	**p-value**	**Hazard Ratio (95% CI)***	**p-value**	**Hazard Ratio (95% CI)***	**p-value**
No sensory impairment	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Single sensory impairment	1.11 (0.86 – 1.44)	0.43	1.10 (0.80 – 1.50)	0.58	1.19 (0.73 – 1.95)	0.48
Dual sensory impairment	1.86 (1.25 – 2.76)	0.002	2.12 (1.34 – 3.36)	0.001	1.22 (0.52 – 2.89)	0.65
Test for trend		0.009		0.01		0.46

CI = Confidence Interval

*Models adjusted for age, sex, race, education, income, body mass index, alcohol intake, smoking status, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, clinic site, treatment status, and ApoE.

Interactions between increasing number of sensory impairments and age, sex, and ApoE were not significant. However, stratification revealed differences; for sex- and ApoE-stratified analyses, DSI was significantly associated with increased risk for all-cause dementia only among females (HR = 2.21; 95% CI = 1.21 – 4.06; P = 0.01) and participants without the ApoE ε4 allele (HR = 2.21; 95% CI = 1.37 – 3.56; P = 0.001) (**Supplemental Table 2.1**). Risk of all-cause dementia associated with DSI appeared to increase with age (<80 years, 80-84 years, and ≥85 years), though estimates were borderline significant for all age groups ($0.05 \leq P \leq 0.08$). Stratifying on baseline cognitive status showed that DSI was associated with risk of all-cause dementia only among those who were cognitively normal at study entry (HR = 2.08; 95% CI = 1.29 – 3.37; P = 0.003) (**Supplemental Table 2.2**).

2.4.2 *Estimated Severity of Sensory Impairments and Differential Associations by Vision and Hearing*

In models evaluating baseline summary scores of DSI and risk of all-cause dementia, significant associations were found for continuous measures (summary score 1-6) and categorization based on three ordered groups of DSI severity (**Table 2.3**). In the fully adjusted model comparing participants with no DSI, those with "high" severity of DSI (defined as having the highest summary score of 5-6) were at the greatest risk of all-cause dementia (HR = 5.09; 95% CI = 1.24 – 20.85; P = 0.02). Participants with "low" severity of DSI (defined as having the lowest summary score of 1-2) were also at significantly increased risk of all-cause dementia (HR = 1.74; 95% CI = 1.04 – 2.90; P = 0.03) compared to participants with no DSI. The dose-response relationship between continuous measures of DSI severity and risk of all-cause dementia was also significant (P_{trend} = 0.02).

Table 2.3. Associations between baseline severity of dual sensory impairment and risk of all-cause dementia

Severity of DSI	Hazard Ratio (95% Confidence Interval)*	p-value
DSI severity (continuous)†	1.15 (1.02 – 1.29)	0.02
DSI severity categories		
No DSI	1.00 (Reference)	
Low (1-2)	1.74 (1.04 – 2.90)	0.03
Intermediate (3-4)	1.30 (0.64 – 2.65)	0.46
High (5-6)	5.09 (1.24 – 20.85)	0.02
Test for trend		0.02

DSI = Dual sensory impairment

*Models adjusted for age, sex, race, education, income, body mass index, alcohol intake, smoking status, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, clinic site, treatment status, and ApoE

†A score of 1-6 was used to define DSI severity. Refer to page 12 for a complete description of how DSI severity scores were defined.

Though single sensory impairment was not associated with risk of dementia as compared with no sensory impairment, associations differed between the type of sensory deficit and dementia risk. Visual impairment was individually associated with risk of all-cause dementia (HR = 1.34; 95% CI = 1.04 – 1.71; *P* = 0.02) and AD (HR = 1.39; 95% CI = 1.03 – 1.87; *P* = 0.03) after adjusting for demographics, health conditions, lifestyle factors, ApoE genotype, and treatment status and clinic site, but not with risk of VaD (**Table 2.4**). With simultaneous inclusion of visual and hearing impairments in one model, visual impairment remained significantly associated with risk of all-cause dementia (HR = 1.32; 95% CI = 1.02 – 1.71; *P* = 0.04), but not with risk of AD or VaD. Hearing impairment was not associated with any dementia outcome whether considered individually or after adjusting for visual impairment in the single model.

Table 2.4. Associations between baseline severity of dual sensory impairment and risk of all-cause dementia

	All-cause dementia				**Alzheimer's disease**				**Vascular dementia**			
	Individual models*		**Combined model***		**Individual models***		**Combined model***		**Individual models***		**Combined model***	
Sensory impairment	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Vision	1.34 (1.04 – 1.71)	0.02	1.32 (1.02 – 1.71)	0.04	1.39 (1.03 – 1.87)	0.03	1.32 (0.97 – 1.80)	0.08	1.24 (0.76 – 2.03)	0.38	1.36 (0.82 – 2.25)	0.23
Hearing	1.18 (0.88 – 1.59)	0.28	1.20 (0.88 – 1.63)	0.25	1.30 (0.92 – 1.85)	0.14	1.31 (0.92 – 1.89)	0.14	0.86 (0.46 – 1.61)	0.64	0.90 (0.48 – 1.69)	0.74

HR = Hazard ratio; CI = Confidence interval; p = p-value

*Models adjusted for age, sex, race, education, income, body mass index, alcohol intake, smoking status, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, clinic site, treatment status, and ApoE.

2.4.3 *Sensitivity Analyses*

Restricting the analysis to probable AD resulted in slightly attenuated estimates for DSI, although the interpretation did not change (**Supplemental Table 2.3**). Including death as a competing risk produced similar associations between DSI and all-cause dementia (**Supplemental Table 2.4**). DSI remained significantly associated with AD when including non-AD as a competing risk (**Supplemental Table 2.4**). Neither DSI nor single sensory impairment were significantly associated with VaD when including non-VaD as a competing risk. Conducting multiple imputation for missing data resulted in attenuated, but still significant, estimates as compared with the complete case analysis. (**Supplemental Table 2.5**).

2.5 DISCUSSION

In this prospective cohort of 2,051 older adults, we found significant associations between DSI and risk of all-cause dementia and AD, but not VaD. In fully adjusted models, DSI was associated with an 86% increased risk for all-cause dementia and an 112% increased risk for AD compared with having no sensory impairments. Greater extent of DSI was also significantly associated with increasing risk of all-cause dementia. These findings were robust after adjustment for multiple potential confounders and in sensitivity analyses. Together, our findings suggest that older adults with DSI represent a high-risk population that could be a target for intervention prior to the onset of dementia.

Previous studies have suggested that associations similar to those reported here might be found. In a cross-sectional study of over 250,000 older adults in China, those with combined vision and hearing impairments had greater odds of dementia than those with no sensory impairment [63].

A longitudinal study with participants from the US and Europe found that older adults with DSI had lower episodic memory scores and remembered fewer words compared with those with no sensory impairment [27]. Another study from Europe examining nursing home residents showed that those with DSI had greater cognitive decline than those with either vision or hearing impairment and those without sensory impairment [28]. A population-based cohort study from Japan using administrative health care data reported that DSI among long-term care recipients was associated with cognitive impairment compared to individuals with normal sensory function [64]. Our study adds to this body of knowledge on the impact of DSI in relation to cognitive impairment by using prospectively collected data in participants followed over eight years, which includes rigorous evaluation of dementia and its main subtypes, AD and VaD.

Several hypotheses can be advanced to explain the link between sensory and cognitive function. Greater impairment in hearing and vision may accelerate cognitive decline because of the association of sensory impairment with social isolation, depression, reduced physical and mental activities, and functional limitations [40]. At a neural level, these impairments may limit or stress the neural resources needed for optimal performance of cognitive tasks by increasing cognitive load [48]. Loss of sensory input can also lead to reduced activation in central sensory pathways, resulting in changes to brain structure and function, such as deafferentation-induced atrophy in frontal brain regions and stressing brain circuitry due to resource demands to address poor signal-to-noise ratios [22,65]. Sensorial stimulation, on the other hand, may have beneficial effects on neuronal development and function, such as formation of new synapses and survival [66]. Alternatively, common pathological processes including vascular disease, inflammation, or some combination of these may be responsible for the relationship between DSI and dementia [41,49]. Hearing and vision loss are associated with vascular pathology, such as white matter hyperintensities and microvascular lesions [67,68], which are also important contributors to VaD. DSI may also be a marker of underlying neurodegeneration. We found that the impact of DSI was strongest for AD. Other studies support a connection between sensory dysfunctions and AD [69], but not all [70,71]. While we accounted for MCI in our analysis, given the long and insidious development of AD, which is also the case for hearing and vision loss, we cannot rule out that reverse causation from early neurodegenerative stages of the AD disease process contributed to the development of DSI. Our findings do not allow a conclusive choice between these hypotheses, which are not mutually exclusive. Additional studies are necessary to determine the mechanisms underlying these associations. Further research is also needed to evaluate whether these mechanisms are shared or differ between hearing and vision as we found that individually visual impairment, but not hearing impairment, was significantly associated with increased risk of all-cause dementia. Either mechanism has implications for potential clinical interventions.

This study has a number of strengths, including its prospective and longitudinal design, large sample size, rigorous classification of dementia and its subtypes, and standardization of data collection for other covariates. Important limitations exist, however, such as misclassification of sensory impairments. The questions used to assess hearing and visual function in the GEM Study were asked at baseline only and their accuracy is unknown. Additionally, information on date of onset and cause of sensory loss were unavailable. The low prevalence of hearing impairment in our sample was likely a result of excluding those with severe hearing loss from participating in the GEM Study and misclassifying some participants who had hearing loss as not having hearing loss. Even with misclassification of hearing impairment that would bias our results towards the null, we still found a significantly increased risk of dementia associated with

DSI, which also accounted for sensory problems in the diagnosis of dementia. Had hearing impairment status been more accurately classified in our study, we would expect an even stronger association between DSI and dementia than what was observed. AD and VaD were classified using standardized clinical criteria and cranial magnetic resonance imaging, but neuropathological information was not available, and again misclassification is possible. However, for the AD outcome, when restricting only to probable AD, which has a higher predictive value of neuropathologic changes in AD as compared with possible AD [72], we did not find substantially different results compared to the primary findings with probable and possible AD included. Another limitation is that our findings may not be generalizable to other populations as participants in the GEM Study were highly selected to be healthy at baseline and were mostly White.

DSI was independently and strongly associated with increased risk of all-cause dementia and AD in this cohort of older adults, but not VaD. Further research is needed to characterize the exact role of sensory impairments and whether treatments that improve sensory function, such as surgery or sensory aids, devices, and prostheses, can modify this risk. As the public health burden of dementia will increase over the next three decades, evaluation of vision and hearing function in older adults may help identify patients at elevated risk of developing dementia.

Chapter 3. ASSOCIATION BETWEEN TIME-VARYING DUAL SENSORY IMPAIRMENT AND RISK OF DEMENTIA IN THE CARDIOVASCULAR HEALTH STUDY

3.1 Background

In older adults, the risk of cognitive decline or impairment [26-29,46,73] and of dementia [63,74,75] are associated with combined hearing and visual impairments, which often occur together as dual sensory impairment (DSI) [45,76]. In prior work, we found an increased risk for all-cause dementia and Alzheimer's disease (AD) associated with DSI among older adults who originally participated in a dementia prevention trial that collected self-reported measures of hearing and visual impairment, along with rigorous ascertainment of dementia [32]. Deficits in hearing and vision may lead to cognitive impairment and dementia by increasing social isolation, depression, and reducing physical activity [22,39,40]. Additionally, sensory and cognitive impairment may share similar, underlying pathophysiology, such as cerebrovascular disease or neurodegeneration [22,41-44,77].

A limitation of these existing studies is that they measured hearing and vision only once at baseline. Modeling sensory impairments longitudinally provides a more accurate reflection of the development of hearing and visual impairment over time, especially as the prevalence of DSI increases with age [7,78,79]. In this study, we investigated associations between hearing and visual impairments in late-life with incident dementia among participants in the Cardiovascular Health Study (CHS), a multi-site longitudinal study of heart disease and stroke in adults 65 years of age and older. CHS collected serial self-reported measurements of hearing and vision during study follow-up, which permitted analysis of hearing and visual impairments as time-varying variables and evaluation of DSI duration on dementia risk. In addition, as part of the CHS Cognition Study, dementia and its major subtypes, AD and vascular dementia (VaD), were adjudicated using research diagnostic criteria, and included neuroimaging. We hypothesized that DSI would be associated with an increased risk of dementia as compared to no or a single sensory impairment in either hearing or vision.

3.2 METHODS

3.2.1 *Study Design and Source Population*

CHS is a population-based prospective study of 5,888 adults at least 65 years of age [80]. In 1989-1990, 5,201 participants were recruited during its initial wave from Medicare eligibility lists in four US communities: Forsyth County, North Carolina; Washington County, Maryland; Sacramento County, California; and Pittsburgh, Pennsylvania [81]. In 1992-1993, 687 predominantly African-American (AA) participants were recruited. From baseline in 1989-1990 until 1998-1999, up to 10 annual clinic visits were completed. Data collected at these examinations each year included demographics, anthropometric measurements, vital signs, cognitive function, information from psychosocial interviews, depression level, medical history, and physical function. Blood samples were collected for genotyping, which included apolipoprotein E (ApoE) genotype [82]. Informed consent was obtained from all participants at entry into the study and at periodic intervals. Institutional review board approval was obtained at all sites collecting and analyzing data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

3.2.2 *Inclusion Criteria and Analytic Sample*

In 1998-1999, dementia was classified in 3,602 participants as part of the CHS Cognition Study (CHSCS) [83]. Inclusion in the CHSCS cohort required completion of cranial magnetic resonance imaging (MRI) and the 100-point modified Mini-Mental State Examination (3MSE) in 1991-1994. These participants were screened using data collected at the visit closest to MRI to identify those who were suspected of having cognitive impairment and asked to return to the clinic for additional cognitive testing. Description of the procedures used to evaluate cognition have been previously published [84]. All prospectively collected data listed above from the inception of CHS were also reviewed to provide additional information on cognitive decline during the 10 years of follow-up. Efforts were made by trained clinical study staff at each cognitive assessment to evaluate hearing and vision problems [85]. This information was recorded so that the effects of poor auditory and visual acuity on the participants' cognitive performance were taken into consideration by the CHSCS adjudication committee [86]. From the CHSCS cohort, we excluded 227 participants with prevalent dementia, as well as an additional 448 participants who were missing information on hearing and vision. Our final analytic sample included 2,927 participants who had available hearing and vision data and were dementia-free at study baseline.

3.2.3 *Exposure of Interest*

Hearing and vision were assessed through self-report at each of the available CHS annual visits from 1989-1990 to 1998-1999, except for visits in 1994-1995 and 1995-1996. Since the baseline visit in CHSCS was between 1991-1994, participants with problems in hearing and vision prior to entry in the CHSCS cohort were considered to have prevalent hearing and visual impairments. Specific questions were asked about hearing and vision (**Supplemental Table 3.1**). Hearing impairment was coded as “1” (yes) if participant was unable to hear well enough to use the phone, listen to the radio, or carry on a conversation in a crowded room, with or without a hearing aid. Visual impairment was coded as “1” (yes) if participant was unable to see well enough to drive, watch TV, recognize someone across a room, or read the newspaper, with or without glasses. Participants classified with hearing impairment and visual impairment at the same visit were defined as having DSI.

3.2.4 *Primary Outcome*

Dementia classification was completed by consensus of a panel of neurologists and psychiatrists using data from neuropsychiatric tests and other data. Dementia was defined using criteria based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [56]. Participants who did not meet dementia criteria, but were failing cognitively were classified as having mild cognitive impairment (MCI), based on previously described criteria [84]. Cranial MRIs were used for classification of dementia subtype. AD was classified using National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer’s Disease and Related Disorders Association criteria [57]. VaD was classified using State of California Alzheimer’s Disease Diagnostic and Treatment Centers criteria [60]. Dementia onset was determined by review of the longitudinal data collected during the 10 years of study follow-up and by family input using the Neuropsychiatric Inventory. If date of onset was determined to be before entry into the CHSCS cohort, the participant was determined to have prevalent dementia at baseline.

3.2.5 *Statistical Analysis*

We summarized baseline characteristics of our sample stratified by number of sensory impairments (0, 1, or, 2) developed over the study period using frequencies and column percentages for categorical variables, and means and standard deviations for continuous variables. For the primary analysis, we examined the associations between number of sensory impairments and incident dementia using time-dependent Cox proportional hazards models, with no sensory impairment as the reference group. Given the longitudinal nature of the study spanning eight years, along with repeated measures of hearing and vision, we created a time-dependent measure to track the change in number of sensory impairments over time for each participant. When developing a new hearing or visual impairment, or both, participants were re-classified to the corresponding category, such as single sensory impairment or DSI, and remain there until end of follow-up, unless a subsequent change in sensory impairment was detected, in which case, sensory impairment status would be ‘up-‘ or ‘down-classified’ to the new category. Time to dementia was calculated as days from baseline to dementia onset, death, or end of CHSCS follow-up. Separate models were developed for all-cause dementia, AD only, and VaD (with or without AD). For each dementia subtype, participants were censored at onset of VaD in models evaluating AD and at onset of AD in models evaluating VaD.

Models were adjusted for baseline covariates, including age, sex, race, education, body mass index, smoking, alcohol intake, physical activity, total cholesterol, diabetes mellitus, hypertension, and ApoE genotype, as well as cohort and clinic site. Cardiovascular disease and cerebrovascular disease were included as time-varying covariates. To identify potential effect modifiers of the association between number of sensory impairments and incident dementia, we stratified participants based on age, sex, and ApoE genotype. We also included interactions terms by age as a continuous variable, and both sex and ApoE genotype as binary variables. Sensitivity analyses included the following: 1) restricting the sample to participants who were cognitively normal and without MCI; and 2) using multiple imputation using chained equations (MICE) to create 20 imputed datasets and comparing results from the imputed data to the primary complete case analysis in order to evaluate potential bias due to missing covariate data [62].

We also examined associations between individual sensory impairments and risk of dementia because associations may differ between types of sensory impairment (hearing versus vision). Hearing and visual impairments were examined in separate models and constructed as discrete time-varying measures, with values of zero prior to and one at times after the development of each sensory impairment. We explored whether a dose-dependent relationship existed between duration of DSI and dementia risk. Duration was modeled as a continuous measure for each year with DSI and as a dichotomized measure, using a cut-off of greater than, or less than or equal to, two years. Estimates for the risk of dementia were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). All *P*-values reported in this study were two-sided with significance at $P < .05$. Analyses were conducted in Stata version 14 (StataCorp, College Station, Texas). Venn/Euler diagrams were created using eulerAPE, which accurately illustrate the overlap of hearing and visual impairments [61].

3.3 RESULTS

Table 3.1 outlines baseline sample characteristics, stratified by number of sensory impairments developed at end of follow-up. Differences were observed in sex, race, education, smoking, and cardiovascular disease at baseline among participants who developed impairments in hearing or vision, or both, compared to those who did not develop hearing or visual impairments.

Table 3.1. Baseline demographics and clinical characteristics according to number of sensory impairments (0, 1, or 2) developed at end of Cardiovascular Health Cognition Study follow-up

Baseline factors	**Overall (n = 2,927)***	**No sensory impairment (n = 2,134)**	**Single sensory impairment (n = 673)**	**Dual sensory impairment (n = 120)**
Age†, mean (SD), years	74.6 (4.8)	74.3 (4.6)	75.4 (5.2)	76.5 (5.2)
Sex, No. (%)				
Female	1,704 (58.2)	1,221 (57.2)	419 (62.2)	64 (53.6)
Male	1,223 (41.8)	913 (42.8)	254 (37.8)	56 (46.4)
Race, No. (%)				
White	2,472 (84.5)	1,810 (84.8)	566 (84.1)	96 (80.0)
Nonwhite	455 (15.5)	324 (15.2)	107 (15.9)	24 (20.0)
Education, No. (%)				
Less than high school	671 (22.9)	452 (21.2)	191 (28.4)	28 (23.3)
High school graduate	838 (28.6)	598 (28.0)	196 (29.1)	44 (36.7)
Some college	711 (24.3)	529 (24.8)	166 (24.7)	16 (13.3)
College graduate	703 (24.0)	553 (25.9)	119 (17.7)	31 (25.8)
Smoking status, No. (%)				
Never	1,390 (47.5)	999 (46.8)	338 (50.2)	53 (44.2)
Former	1,221 (41.7)	902 (42.3)	258 (38.3)	61 (50.8)
Current	306 (10.4)	226 (10.6)	74 (11.0)	6 (5.0)

Alcohol intake, mean (SD), drinks/week	2.7 (6.5)	2.8 (6.8)	2.2 (5.5)	3.0 (5.9)
Body mass index, mean (SD), kg/m^2	26.5 (4.3)	26.6 (4.3)	26.4 (4.2)	26.0 (4.9)
Physical activity, No. (%)				
No exercise	256 (8.7)	175 (8.2)	69 (10.2)	12 (10.0)
Low exercise	1,239 (42.3)	890 (41.7)	303 (45.0)	46 (38.3)
Moderate exercise	1,114 (38.0)	819 (38.4)	245 (36.4)	50 (41.7)
High exercise	310 (10.6)	243 (11.4)	56 (8.3)	11 (9.2)
Diabetes mellitus, No. (%)				
Normal	2,141 (73.1)	1,571 (73.6)	477 (70.9)	93 (77.5)
Impaired fasting glucose	393 (13.4)	290 (13.6)	86 (12.8)	17 (14.2)
Diabetes mellitus	372 (12.7)	258 (12.1)	104 (15.4)	10 (8.3)
Hypertension, No. (%)				
Normal	1,324 (45.2)	979 (45.9)	293 (43.5)	52 (43.3)
Borderline	404 (13.8)	309 (14.5)	91 (13.5)	4 (3.3)
Hypertensive	1,183 (40.4)	843 (39.5)	289 (42.9)	51 (42.5)
Cardiovascular disease[‡], No. (%)	516 (17.6)	356 (16.7)	130 (19.3)	30 (25.0)
Cerebrovascular disease[§], No. (%)	120 (4.1)	77 (3.6)	37 (5.5)	6 (5.0)
Total cholesterol[¶], mean (SD), mg/dL	211.4 (38.1)	211.5 (38.2)	211.2 (37.8)	210.2 (39.1)
ApoE genotype, No. (%)				
Presence of ≥1 ε4 allele	637 (21.8)	467 (21.9)	143 (21.2)	27 (22.5)
No ε4 allele	2,051 (70.1)	1,500 (70.3)	472 (70.1)	79 (65.8)

ApoE = Apolipoprotein E; kg/m^2 = kilograms per meter squared; mg/dL = milligrams per deciliter; No. = number; SD = Standard deviation

[*]Column totals may not add up to 100% due to missing observations: Education, n = 4 (0.14%); Smoking status, n = 10 (0.34%); Alcohol intake, n = 10 (0.34%); Body mass index, n = 7 (0.24%); Physical activity, n = 8 (0.27%); Diabetes mellitus, n = 21 (0.72%); Hypertension, n = 16 (0.55%); Total cholesterol, n = 16 (0.55%); ApoE genotype, n = 239 (8.2%); [†]Age = Age at MRI; [‡]Cardiovascular disease defined as prevalent angina, congestive heart failure, coronary heart disease, claudication, or myocardial infarction at baseline; [§]Cerebrovascular disease defined as prevalent stroke or transient ischemic attack at baseline; [¶]To convert total cholesterol from milligrams per deciliter to millimoles per liter, multiply by 0.0259.

Figure 3.1 describes the distribution of hearing and visual impairments by end of the study. Most participants (72.9%) did not develop hearing or vision impairments, while about four percent of participants developed DSI. Slightly more participants developed visual impairment only (12.4%) as compared with hearing impairment only (10.6%).

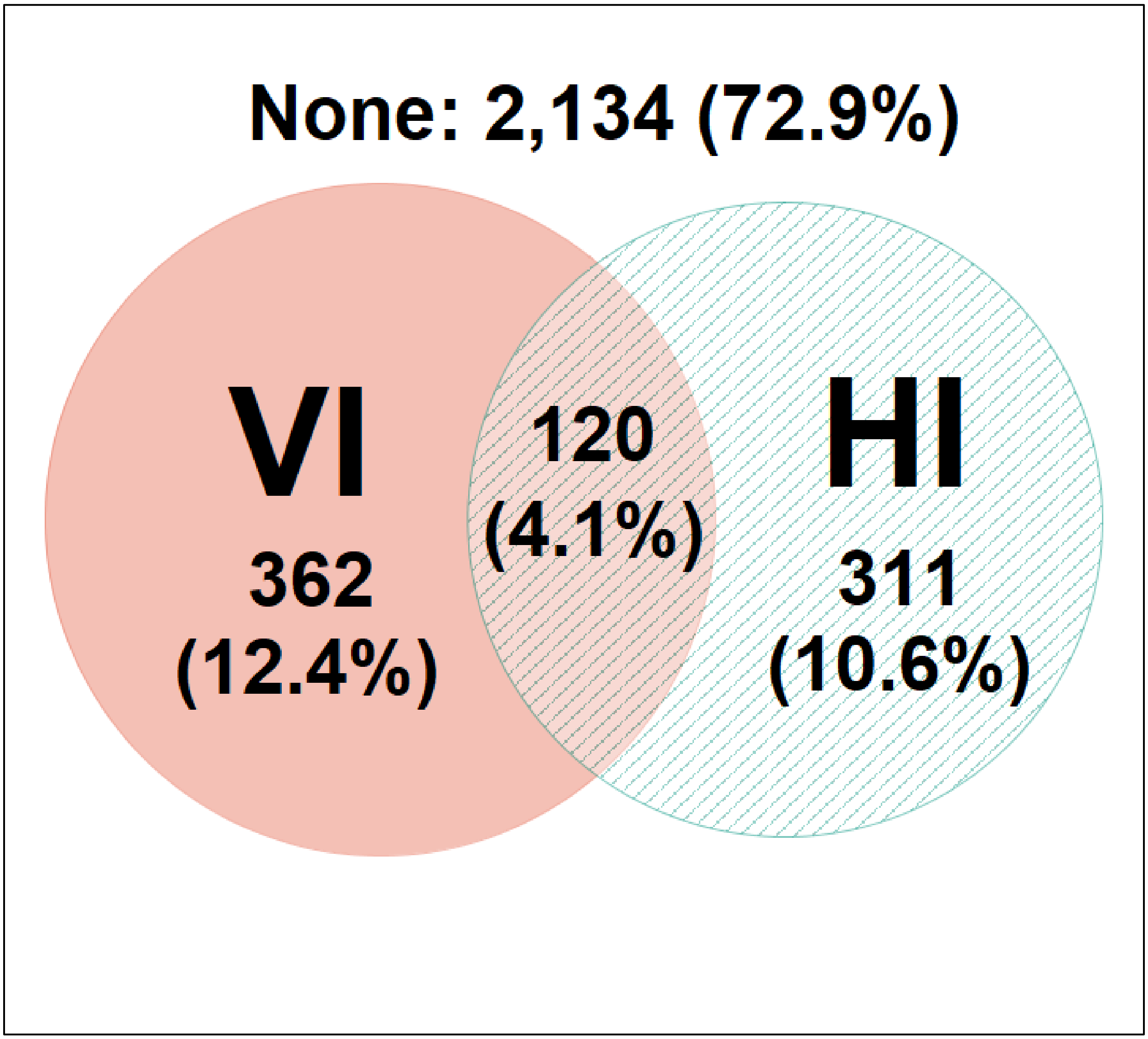

Figure 3.1. Development of visual impairment (VI) and hearing impairment (HI), or both, at end of Cardiovascular Health Cognition Study follow-up

3.3.1 *Time-Varying Sensory Impairments and Associations with Dementia*

Over 14,455 person-years of follow-up, 307 participants (10.5%) developed dementia. **Table 3.2** displays results from Cox models examining the association between time-varying number of sensory impairments and risk of dementia. In adjusted models, DSI was associated with significantly increased risk for all-cause dementia (HR = 2.60; 95% CI = 1.66 – 4.06) and AD (HR = 3.67; 95% CI = 2.04 – 6.60). Single sensory impairment was also significantly associated with risk for all-cause dementia and AD, though compared with DSI, estimates were attenuated (all-cause dementia, HR = 1.72 [95% CI = 1.34 – 2.21]; AD, HR = 2.32 [95% CI = 1.63 – 3.29]). Neither DSI nor single sensory impairment was significantly associated with increased risk for VaD in adjusted models.

Table 3.2. Associations between number of sensory impairments and risk of dementia, including Alzheimer's disease and vascular dementia, in Cardiovascular Health Cognition Study (1991 – 1999)

	All-cause dementia (n = 307)				**Alzheimer's disease (n = 153)**				**Vascular dementia (n = 144)**			
	Model 1*		**Model 2†**		**Model 1***		**Model 2†**		**Model 1***		**Model 2†**	
Number of Sensory Impairments	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
No sensory impairment	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Single sensory impairment	2.18 (1.76 – 2.71)	<.001	1.72 (1.34 – 2.21)	<.001	2.69 (1.98 – 3.64)	<.001	2.32 (1.63 – 3.29)	<.001	1.77 (1.27 – 2.47)	.001	1.38 (0.95 – 2.01)	.09
Dual sensory impairment	4.06 (2.79 – 5.90)	<.001	2.60 (1.66 – 4.06)	<.001	4.96 (2.98 – 8.25)	<.001	3.67 (2.04 – 6.60)	<.001	3.71 (2.12 – 6.51)	<.001	2.03 (1.00 – 4.09)	.05
Test for trend		<.001		<.001		<.001		<.001		<.001		.02

HR = Hazard Ratio; CI = Confidence Interval; *Univariable models; †Multivariable models adjusted for age, sex, race, education, body mass index, alcohol intake, smoking status, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, total cholesterol, cohort, clinic site, and ApoE.

Results from the primary analysis did not change substantially based on sensitivity analyses that excluded participants with MCI (**Supplemental Table 3.2**) and imputed missing covariates using MICE (**Supplemental Table 3.3**). Examination of age, sex, and ApoE genotype as potential effect modifiers (**Supplemental Table 3.4**) revealed age- and ApoE-specific associations, with significant statistical interactions between increasing number of sensory impairments and age (P <.001), and ApoE genotype (P = .02). Estimates were not appreciably different between women and men.

3.3.2 *Associations with Individual Sensory Impairments and with Duration of Dual Sensory Impairment*

We examined associations by individual sensory impairments (**Table 3.3**) and found that hearing and vision loss were both independently associated with increased risk for all-cause dementia (hearing, HR = 1.53 [95% CI = 1.20 – 1.97]; vision, HR = 1.28 [95% CI = 1.02 – 1.60]) and AD (hearing, HR = 1.54 [95% CI = 1.09 – 2.18]; vision, HR = 1.48 [95% CI = 1.08 – 2.01]). Only hearing impairment was independently associated with VaD (HR = 1.66; 95% CI = 1.16 – 2.38).

Table 3.3. Associations between individual sensory impairments (vision and hearing) and risk of incident all-cause dementia, Alzheimer's disease, and vascular dementia

	All-cause dementia		**Alzheimer's disease**		**Vascular dementia**	
Sensory impairment	**Hazard ratio (95% CI)***	***P*-value**	**Hazard ratio (95% CI)***	***P*-value**	**Hazard ratio (95% CI)***	***P*-value**
Vision	1.28 (1.02 – 1.60)	.03	1.48 (1.08 – 2.01)	.01	1.09 (0.77 – 1.55)	.62
Hearing	1.53 (1.20 – 1.97)	.001	1.54 (1.09 – 2.18)	.02	1.66 (1.16 – 2.38)	.006

CI = Confidence interval; *Models adjusted for age, sex, race, education, body mass index, alcohol intake, smoking status, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, total cholesterol, cohort, clinic site, and ApoE.

Table 3.4 describes the association between DSI duration and risk of dementia. Each additional year with DSI was associated with a 31% increased risk for all-cause dementia (HR = 1.31; 95% CI = 1.07 – 1.62) and 46% increased risk for AD (HR = 1.46; 95% CI = 1.12 – 1.91). Participants with DSI for more than two years were at greater risk for all-cause dementia (HR = 1.61; 95% CI = 1.04 – 2.53) and AD (HR = 1.96; 95% CI = 1.11 – 3.50) as compared to participants without DSI, whereas no significant associations were observed with duration of DSI less than or equal to two years.

Table 3.4. Association between duration of dual sensory impairment and risk of dementia, including Alzheimer's disease and vascular dementia

	All-cause dementia		**Alzheimer's disease**		**Vascular dementia**	
Duration of dual sensory impairment	**Hazard Ratio (95% CI)***	***P*-value**	**Hazard Ratio (95% CI)***	***P*-value**	**Hazard Ratio (95% CI)***	***P*-value**
DSI duration (continuous)†	1.31 (1.07 – 1.62)	.02	1.46 (1.12 – 1.91)	.01	1.20 (0.86 – 1.68)	.35
DSI duration (categorical)						
No DSI (n = 2,807)	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
DSI ≤2 years (n = 61)	1.48 (0.92 – 2.39)	.11	1.55 (0.82 – 2.98)	.20	1.28 (0.60 – 2.73)	.55
DSI >2 years (n = 59)	1.61 (1.04 – 2.53)	.03	1.96 (1.11 – 3.50)	.02	1.52 (0.74 – 3.11)	.26

CI = Confidence Interval; DSI = Dual Sensory Impairment; *Models adjusted for age, sex, race, education, body mass index, alcohol intake, smoking status, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, total cholesterol, cohort, clinic site, and ApoE; †Risk associated with a 1 year difference in duration of dual sensory impairment.

3.4 DISCUSSION

In this study, we found that greater number of sensory impairments was associated with increased risk of dementia among older adults in CHSCS. DSI was associated with a greater than three times increased risk for AD compared to no sensory impairment. By using serial measurements of hearing and vision over a follow-up period of up to eight years, we incorporated changes in sensory function that better reflect the impact of increasing burden of hearing and visual deficits on dementia risk. These findings may be relevant to the clinical setting where evaluation of hearing and vision in older adults is ongoing, as well as support the notion that older adults with DSI represent a high-risk group for developing dementia, especially AD.

Our study contributes to the existing literature examining the impact of multiple sensory impairments on accelerated cognitive aging. Previous studies found that multiple deficits in sensory function, including vision, hearing, and olfaction, have a greater impact on cognitive decline or impairment than a single sensory deficit [87,88]. These results suggest that there are additive effects of multiple sensory impairments on dementia risk. Two recent studies from the Health, Aging, and Body Composition Study showed that multisensory impairment was strongly associated with increased risk of dementia [50], with worsening multisensory function, even at mild levels, associated with higher risk of dementia and faster rates of cognitive decline [89]. Using longitudinal measures of hearing and vision collected in CHS, we extend these findings to show that longer duration of DSI is also associated with increased risk of dementia.

We found that individual impairments in hearing and vision were independently associated with incident dementia. Other studies that examined hearing and vision separately found that each sensory impairment was associated with increased risk of dementia [17-19,38]. Changes in sensory function have also been shown to predict changes in cognitive performance [90]. However, whether hearing and visual impairments impact cognition similarly is not clear. Some studies reported that decline in vision, compared with hearing, was a more consistent and pronounced predictor of cognitive changes [91,92], but other studies found that only hearing was associated with cognitive decline [93]. Many of the effects of DSI are thought to be mediated primarily by vision loss in that hearing impairment has not been shown to add to the likelihood of depression [94,95], functional impairment [96,97], or cognitive decline [74]. Findings from these studies suggest that the added presence of hearing loss does not further diminish abilities above and beyond those of visual impairment alone among individuals with DSI. Studies examining the comparative effects of hearing loss and vision loss hypothesize that vision is most immediately necessary for interaction with the physical and spatial world, while hearing is most needed with the social world [98-100]. Additional research is needed to understand how the effects of hearing loss and vision loss differ in DSI and their interaction in relation to cognitive function.

Several hypotheses have been proposed to explain the relationship between sensory and cognitive function. The sensory deprivation hypothesis postulates that prolonged reductions in sensory input lead to cognitive deterioration due to neuronal atrophy [90,101,102]. Sensory impairment has been linked to social isolation, depression, reduced physical and mental activities, and functional limitations [40,33,103]. Loss of sensory input may also lead to reduced activation in central sensory pathways, resulting in changes to brain structure and function [22,65]. Results from observational studies that examined interventions in sensory ability, such as cataract surgery and hearing aids, provide some preliminary support of a causal relationship between sensory impairment and cognition as they found associations with slower cognitive decline [104,105]. The cognitive load hypothesis theorizes that cognitive decline may lead to decline in sensory performance because cognitive dysfunction reduces the cognitive resources available for sensory perception [101,106]. For example, speech recognition among individuals with hearing impairment may be more challenging, which may limit or stress the neural resources needed for optimal performance of cognitive tasks, thereby leading to increased perceptual and cognitive load compared to those with normal hearing function [48]. The common cause hypothesis states that associations between sensory functioning and cognitive ability reflect shared pathological processes, such as vascular disease, inflammation, or some combination of common age-related factors [41,101,49,67,68], as well as genetics, including ApoE [107,108].

This study has several strengths, including large sample size and well-characterized CHS data. CHS also collected information on hearing and vision at multiple study visits, and therefore we were able to account for changes in sensory impairment over time and evaluate whether duration of DSI is associated with dementia risk, which is an important contribution to the literature. Several limitations to this work are worth noting. First, the accuracy of the questions used to assess hearing and visual function in CHS is unknown, which may result in misclassification of sensory impairment status. Our results though are consistent with previous studies that used objective tests for hearing and visual function in evaluating associations with dementia

[18,20,109-111]. Future studies should nonetheless evaluate the sensitivity and specificity of these self-reported measures against objective measures of hearing and vision. Second, methods used to ascertain dementia and date of onset in CHSCS were non-traditional and may have resulted in misclassification. This type of error would most likely attenuate associations toward the null, however, and not affect the overall conclusions. Difficulties in sensory perception could result in poor performance on neuropsychological tests [101,112], leading to possible misclassification of dementia. This risk was minimized though in CHSCS since the adjudication committee accounted for any hearing or vision problems during cognitive testing and reviewed multiple sources of information during its assessment of dementia. Third, the results of this study are relevant only to those who live beyond age 65 years without dementia, and generalizations should be made only to this group.

Taken together, these data suggest that older adults with DSI are at an elevated risk of developing dementia, particularly AD. Additional studies are needed to understand whether sensory impairments are a causal risk factor for dementia, or a marker of incipient dementia. Interventions targeting hearing and vision loss, such as surgery or sensory aids, devices, and prostheses, may help attenuate dementia risk. With the public health burden of dementia expected to increase in the coming decades [113], our findings suggest that evaluation of vision and hearing should play an important role in preventive strategies for dementia.

Chapter 4. ASSOCIATIONS BETWEEN SPECIFIC OPHTHALMIC CONDTIONS AND RISK OF DEMENTIA IN THE CARDIOVASCULAR HEALTH STUDY

4.1 BACKGROUND

Dementia is a major cause of disability and dependency among older populations [21]. The most common causes of dementia include Alzheimer's disease (AD) and vascular dementia (VaD) [114]. Despite extensive research, many aspects of their pathophysiology and clinical course remain unknown. Better understanding of disease mechanisms, predictors, and risk factors may lead to early detection and preventive measures.

The brain and the eye share many characteristics, including embryologic origin, precise neuronal cell layers, complex neurochemistry and neurotransmitter systems, microglia, astroglia, blood barriers, and microvasculature [30]. As an extension of the central nervous system, the eye may offer opportunities to capture critical information on the health of the brain. Animal and imaging studies suggest that cataracts, glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (DR) may be associated with dementia due to shared characteristics, such as progressive neurodegeneration, characteristic β-amyloid (Aβ) deposits, and chronic microvascular lesions [23,31]. The eye, unlike the brain, can be examined physically *in vivo*, and may provide a window into processes in the brain.

Findings from previous epidemiologic studies that examined associations between glaucoma, AMD, or DR and dementia have been inconsistent [86,115-121]. Very few studies have investigated the relative associations of all these ophthalmic conditions with risk for various types of dementia, and have not included cataracts as predictors. One recent prospective cohort study found that glaucoma, AMD, and DR were associated with the clinical development of AD, but cataracts were not associated with AD or all-cause dementia [122]. Despite the contribution of vascular disease to dementia and retinal disorders [123,124], knowledge about the relationships between these ophthalmic conditions and VaD is also limited. The Cardiovascular Health Study (CHS) allowed us to quantify associations between these specific ophthalmic conditions and dementia because it had reliable methods of ascertainment. It identified diagnoses of common ophthalmic conditions by medical records, including linkage to participants' Medicare Part B records, which allowed capture of outpatient-based diagnoses not collected by CHS. The major dementia subtypes, AD and VaD, were adjudicated using research diagnostic criteria, and included neuroimaging. We sought to evaluate associations between cataracts, glaucoma, AMD, and DR and risk of all-cause dementia, AD, and VaD.

4.2 METHODS

CHS is a population-based prospective study of 5,888 adults 65 years and older [80]. In 1989-1990, 5,201 participants were recruited into CHS during its initial wave from Medicare eligibility lists in four US communities [81]. In 1992-1993, 687 predominantly African-American (AA) participants were recruited. Informed consent was obtained from all the participants at entry into the study and at periodic intervals. Institutional review board approval was obtained at all sites collecting and analyzing data.

4.2.1 *Data Collection*

From baseline in 1989-1990 until 1998-1999, up to 10 annual clinic visits were completed. Data collected at these examinations each year included demographics, anthropometric measurements, vital signs, cognitive function, information from psychosocial interviews, depression level, medical history, and physical function. Genotyping of apolipoprotein E (ApoE) was performed from a blood sample.

4.2.2 *Assessment of Cognitive Function and Dementia*

In 1998-1999, dementia was classified in 3,602 participants as part of the CHS Cognition Study [83]. Inclusion in the CHS Cognition Study cohort required completion of cranial magnetic resonance imaging (MRI) and the 100-point modified Mini-Mental State Examination (3MSE) in 1991-1994 (**Figure 4.1**).

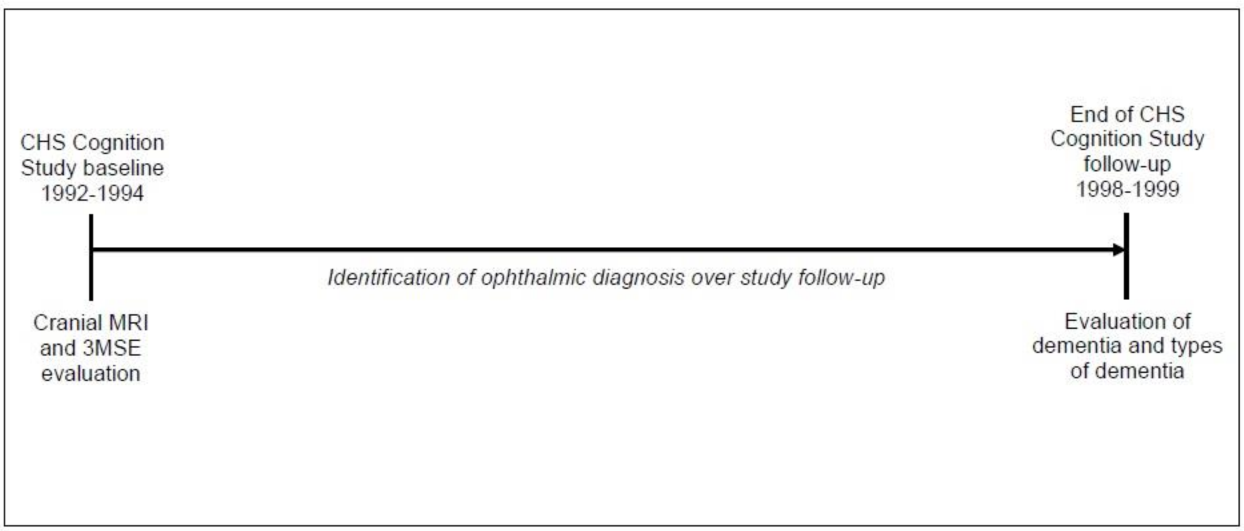

Figure 4.1. Timeline of the Cardiovascular Health Study-Cognition Study.

These participants were screened using data collected at the visit closest to MRI to identify those who were suspected of having cognitive impairment and who were asked to return to the clinic for additional cognitive testing. Description of the procedures used to evaluate cognition have been published previously [84]. All prospectively collected data listed above from the inception of the CHS were also reviewed to provide additional information on cognitive decline during the 10 years of follow-up. Efforts were made by trained clinical study staff at each cognitive assessment to evaluate vision problems [85]. This information was recorded so that the effects of poor visual acuity in the participants' cognitive performance were taken into consideration by the CHS Cognition Study adjudication committee [86].

Dementia classification was completed by consensus of a panel of neurologists and psychiatrists using data from the neuropsychiatric tests and other data, which have been described elsewhere [84]. Dementia was defined using criteria similar to the one used in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [56]. Participants who did not meet the dementia criteria, but showed cognitive deficits based on neuropsychological evaluation were classified as having mild cognitive impairment (MCI). Those with MCI presented memory deficits, defined as performance more than 1.5 standard deviations below that of participants of comparable age and education; deterioration in other cognitive domains, such as language, executive functioning, and visuoconstructional abilities; one abnormal test in at least two cognitive domains, without sufficiently severe cognitive impairment, or loss of activities of daily living to constitute dementia [84]. Cranial MRIs were used for classification of dementia subtype. AD was classified using National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association criteria [57]. VaD was classified using State of California Alzheimer's Disease Diagnostic and Treatment Centers criteria [60]. Dementia onset was determined by review of the longitudinal data collected during the 10 years of study follow-up and by family input using the Neuropsychiatric Inventory. If the date of onset was determined to be before entry into the CHS Cognition Study cohort, the participant was determined to have prevalent dementia at baseline.

4.2.3 *Diagnosis of Ophthalmic Conditions*

Specific ophthalmic conditions included cataracts, glaucoma, AMD, and DR. The presence of these conditions (yes, no) was based on International Classification of Diseases, 9th revision (ICD-9) codes: cataracts (366.*), glaucoma (365.*, except 365.0*), AMD (362.50, 362.51, 362.52), and DR (362.0*). We also used information from medical histories collected at the first follow-up visit in CHS (and baseline visit for the AA cohort) to determine prevalent cataracts, glaucoma, and retinal diseases within the CHS Cognition Study cohort. In CHS, diagnostic codes were based on hospital discharge and inpatient services, and therefore may represent only advanced eye disease, which would result in a biased sample. To address this limitation, we used linked outpatient and physician/carrier claims data from Medicare Part B to identify diagnoses of ophthalmic conditions not available through the inpatient-based records in CHS. CHS participants were matched to Medicare enrollment and claims data, which were available through 2015, by their social security number, sex, and date of birth. A non-informative study identification number unique to each CHS participant facilitated linkage of Medicare Part B claims data to CHS data.

4.2.4 *Statistical Analysis*

Of the 3,602 participants in the CHS Cognition Study cohort, 227 with prevalent dementia on MRI were excluded. We tabulated descriptive statistics for demographics and comorbidities by each ophthalmic condition individually and by those who developed any ophthalmic condition compared to none. Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) to estimate the risk of dementia associated with cataracts, glaucoma, AMD, and DR. Participant age was used as the time axis to control more finely for age as a potential confounder. Examination of the proportionality assumption was done using Schoenfeld residuals. Time to dementia was calculated as days from baseline to dementia onset, death, or end of CHS Cognition Study follow-up. Each ophthalmic condition was modeled as a binary time-varying covariate, equal to 0 at times prior to and 1 after the diagnosis, and was included in separate models, as well as in a combined model to adjust for the presence of other ophthalmic conditions. Time at risk was calculated separately for each covariate value (0 or 1) assumed by the participant. At any given time, participants without any of the specific ophthalmic conditions served as the reference group. All-cause dementia, probable or possible AD (without VaD), and probable or possible VaD (with or without AD) were the outcomes of interest. For dementia subtype, persons were censored at onset of VaD in models evaluating AD and for AD in models evaluating VaD.

Models were adjusted for demographics (age at entry as a continuous variable, sex, race, and education) and cardiovascular and dementia risk factors (body mass index, smoking, alcohol intake, physical activity, total cholesterol, diabetes mellitus, hypertension, history of cardiovascular disease, history of cerebrovascular disease, and ApoE genotype), which were all measured at baseline, as well as cohort and clinic site. We also included self-reported income and accessibility to medical care, refractive errors (presbyopia, astigmatism, hypermetropia, and myopia), inflammatory markers (C-reactive protein level and interleukin-6 level), and treatments for cataracts, glaucoma, AMD, or DR as covariates in additional models. Diagnosis of refractive errors were based on ICD-9 codes and treatment of specific ophthalmic conditions, such as cataract surgery, were based on Current Procedural Terminology codes (**Supplemental Table 4.1**). To identify potential effect modifiers of the association between dementia and each ophthalmic condition, we stratified participants based on age, sex, and ApoE genotype. Age was dichotomized as <80 years or ≥80 years as the prevalence of these ophthalmic conditions is highest among individuals aged ≥80 years. To assess for possible interaction, we also included in the models, interaction terms for each ophthalmic condition by age as a continuous variable, and both sex and ApoE genotype as binary variables. Finally, to evaluate potential bias due to: (1) competing risks, we used the sub-distribution hazard function; and (2) missing covariate data, we used multiple imputation using chained equations to create 20 imputed datasets [62]. All *P*-values reported in this study were two-sided with significance at $P < 0.05$. Analyses were conducted using Stata version 15.1 (StataCorp, College Station, Texas).

4.3 RESULTS

Of the 3,375 participants included in the analyses, 480 were classified with incident all-cause dementia during an average of 4.1 years of follow-up. Of these, 245 were determined to have AD only and 213 were determined to have VaD, with or without AD. Average age of participants was 74.8 years, ranging from 65 through 97 years. More than half of participants were women and 87.3% were white. Approximately 83% of the sample developed at least one ophthalmic condition (cataracts, glaucoma, AMD, DR), whereas 17% did not develop any of these conditions during the study period. Most participants developed cataracts (1,113 incident; 1,503 prevalent), followed by AMD (465 incident; 203 prevalent) and glaucoma (311 incident; 290 prevalent), while the least number of participants developed DR (162 incident; 39

prevalent). **Table 4.1** describes characteristics of the study sample by each ophthalmic condition. Comparing across participants who developed cataracts, glaucoma, AMD, or DR, significant differences were found by age, race, alcohol intake, BMI, diabetes mellitus, hypertension, and ApoE genotype. Participants who developed at least one of these ophthalmic conditions tended to be white, more educated, and have no history of smoking and no ε4 allele as compared to participants who did not develop any of these conditions (**Supplemental Table 4.2**).

Table 4.1. Demographic and baseline clinical factors by each ophthalmic condition (cataracts, AMD, DR, glaucoma) at end of follow-up in the CHS Cognition Study*

Baseline factors†	**Cataract diagnosis (n = 2,616)**	**AMD diagnosis (n = 668)**	**DR diagnosis (n = 201)**	**Glaucoma diagnosis (n = 601)**	**No diagnosis of cataract, AMD, DR, or glaucoma (n = 571)**
Age‡, mean (SD), years	74.9 (4.9)	76.1 (5.3)	74.3 (4.3)	75.2 (4.8)	74.4 (4.9)
Sex, No. (%)					
Female	1,532 (58.6)	387 (57.9)	119 (59.2)	350 (58.2)	327 (57.3)
Male	1,084 (41.4)	381 (42.1)	82 (40.8)	251 (41.8)	244 (42.7)
Race, No. (%)					
White	2,284 (87.3)	623 (93.3)	154 (76.6)	501 (83.4)	410 (71.8)
Nonwhite	332 (12.7)	45 (6.7)	47 (23.4)	100 (16.6)	161 (28.2)
Education, No. (%)					
Less than high school	613 (23.5)	176 (26.4)	55 (27.5)	138 (23.1)	146 (25.6)
High school graduate	736 (28.2)	185 (27.7)	62 (31.0)	158 (26.4)	181 (31.8)
Some college	640 (24.5)	166 (24.9)	45 (22.5)	153 (25.6)	126 (22.1)
College graduate	624 (23.9)	140 (21.0)	38 (19.0)	149 (24.9)	117 (20.5)
Smoking status, No. (%)					
Never	1,246 (47.7)	319 (47.8)	100 (49.8)	290 (48.3)	258 (45.2)
Former	1,094 (41.9)	273 (40.9)	81 (40.3)	250 (41.7)	232 (40.6)
Current	272 (10.4)	76 (11.4)	20 (10.0)	60 (10.0)	81 (14.2)
Alcohol intake, mean (SD), drinks/week	2.8 (13.7)	2.3 (6.0)	1.6 (4.4)	2.6 (5.7)	3.0 (7.6)
Body mass index, mean (SD), kg/m^2	26.5 (4.4)	26.1 (4.3)	27.8 (4.7)	26.2 (4.2)	26.7 (4.2)
Physical activity, No. (%)					
No exercise	163 (6.2)	55 (8.2)	12 (6.0)	42 (7.0)	32 (5.6)
Low exercise	1,176 (45.0)	301 (45.1)	94 (46.8)	261 (43.4)	254 (44.5)
Moderate exercise	954 (36.5)	236 (35.4)	74 (36.8)	229 (38.1)	226 (39.6)
High exercise	321 (12.3)	75 (11.2)	21 (10.4)	69 (11.5)	59 (10.3)
Diabetes mellitus, No. (%)					

Normal	1,928 (74.3)	498 (74.9)	65 (32.7)	438 (73.4)	401 (70.7)
Impaired fasting glucose	329 (12.7)	76 (11.4)	19 (9.6)	87 (14.6)	88 (15.5)
Diabetes mellitus	339 (13.1)	91 (13.7)	115 (57.8)	72 (12.1)	78 (13.8)
Hypertension, No. (%)					
Normal	1,197 (45.8)	296 (44.4)	70 (34.8)	270 (44.9)	234 (41.0)
Borderline	354 (13.6)	95 (14.2)	23 (11.4)	78 (13.0)	101 (17.7)
Hypertensive	1,062 (40.6)	276 (41.4)	108 (53.7)	253 (42.1)	236 (41.3)
Cardiovascular disease§, No. (%)	436 (16.7)	131 (19.6)	45 (22.4)	98 (16.3)	99 (17.3)
Cerebrovascular disease¶, No. (%)	103 (3.9)	26 (3.9)	11 (5.5)	20 (3.3)	29 (5.1)
Total cholesterol#, mean (SD), mg/dL	211.6 (38.2)	210.3 (38.6)	203.0 (38.0)	210.1 (37.3)	210.4 (39.3)
ApoE genotype, No. (%)					
Presence of ε4 allele	564 (23.6)	124 (20.1)	50 (27.5)	125 (22.8)	140 (24.5)
No ε4 allele	1,822 (76.4)	493 (79.9)	132 (72.5)	422 (77.2)	384 (67.2)

AMD = Age-related macular degeneration; ApoE = Apolipoprotein E; DR = Diabetic retinopathy; SD = Standard deviation; kg/m^2 = kilograms per meter squared; mg/dL = milligrams per deciliter

*Participants could develop more than one ophthalmic condition, so the column totals do not represent mutually exclusive groups; †Information was collected around the time of the cranial MRI between 1992 and 1994, and was missing for some variables as follows: Education: n = 5 (0.15%), Smoking status: n = 4 (0.12%), Alcohol intake: n = 13 (0.38%), Body mass index: n = 9 (0.27%), Physical activity: n = 2 (0.06%), Diabetes mellitus: n = 25 (0.74%), Hypertension: n = 3 (0.09%), ApoE genotype: n = 286 (8.5%); ‡Age = Age at MRI; §Cardiovascular disease defined as prevalent angina, congestive heart failure, coronary heart disease, claudication, or myocardial infarction at baseline; ¶Cerebrovascular disease defined as prevalent stroke or transient ischemic attack at baseline; #To convert total cholesterol from milligrams per deciliter to millimoles per liter, multiply by 0.0259

4.3.1 *Associations between Specific Ophthalmic Conditions and Risk of Dementia*

Cataracts, AMD, and DR, but not glaucoma, at baseline in the CHS Cognition Study were significantly associated with risk of all-cause dementia based on crude Kaplan-Meier estimates (**Figure 4.2**).

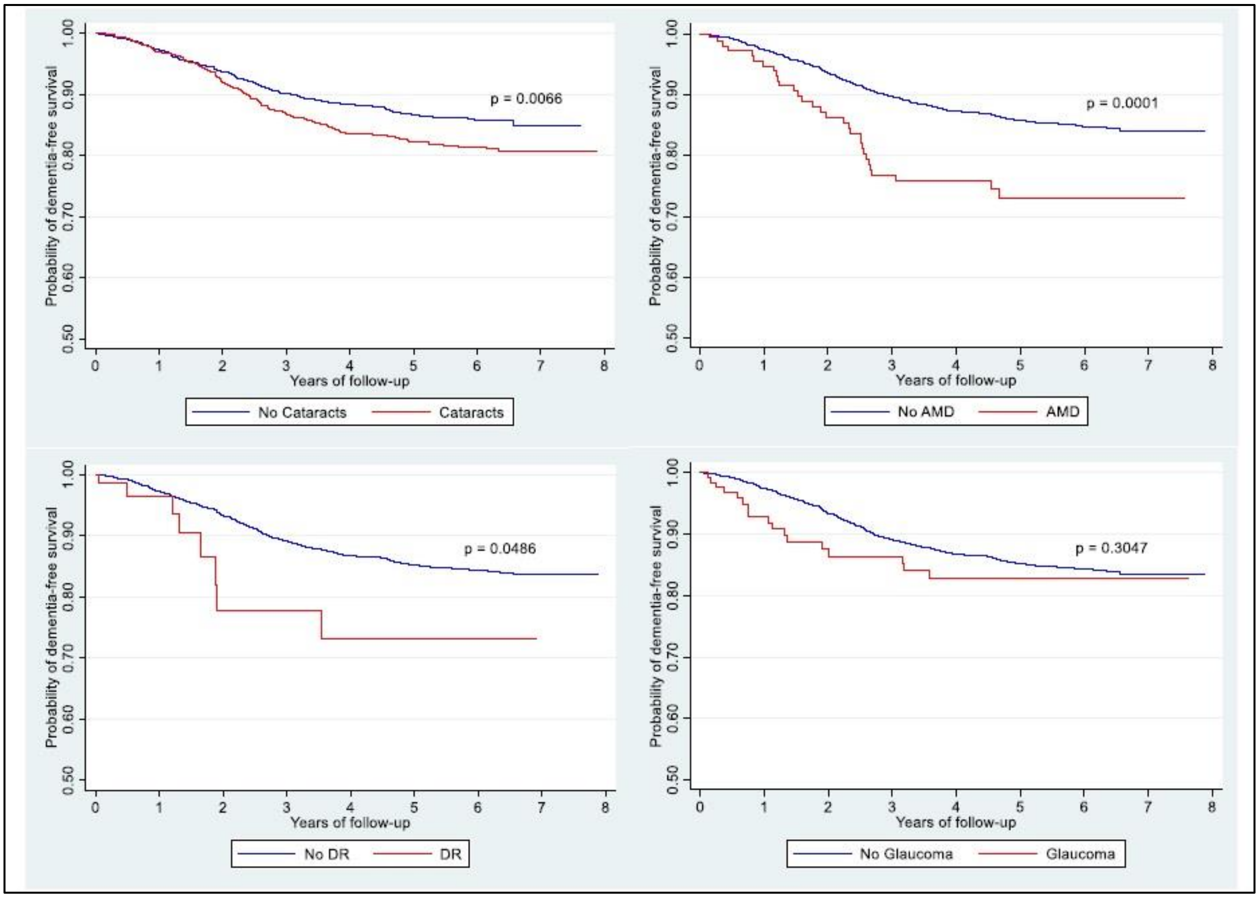

Figure 4.2. Survival curves for cataracts, AMD, DR, and glaucoma at study baseline from the primary (individual) models for all-cause dementia.

In adjusted models for demographics and cardiovascular and dementia risk factors, as well as cohort and clinic site (**Table 4.2**), risk of all-cause dementia was associated with cataracts (HR = 1.38; 95% CI = 1.10 – 1.72; *P* = 0.005) and AMD (HR = 1.57; 95% CI = 1.07 – 2.30; *P* = 0.021) compared to those without any ophthalmic condition. Also, cataracts and AMD were associated with a 34% (HR = 1.34; 95% CI = 1.01 – 1.80; *P* = 0.039) and 87% (HR = 1.87; 95% CI = 1.13 – 3.09; *P* = 0.014) increased risk of AD, respectively. DR and glaucoma were not significantly associated with risk of all-cause dementia or AD. DR was associated with risk for VaD (HR = 2.63; 95% CI = 1.10 – 6.27; *P* = 0.029). Cataracts also increased risk of VaD (HR = 1.41; 95% CI = 1.02 – 1.95; *P* = 0.037). AMD and glaucoma were not significantly associated with risk of VaD.

Table 4.2. Risk of all-cause dementia, Alzheimer's disease, and vascular dementia in the individual (each ophthalmic condition modeled separately) models, with reference group as those without cataracts, AMD, DR, and glaucoma

Outcome and Specific Ophthalmic Condition	**Model 1***		**Model 2†**	
All-cause dementia (n = 480)	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Cataracts (n = 2,616)	1.26 (1.03 – 1.54)	0.026	1.38 (1.10 – 1.72)	0.005
AMD (n = 668)	1.49 (1.03 – 2.14)	0.033	1.57 (1.07 – 2.30)	0.021
DR (n = 201)	1.42 (0.67 – 3.00)	0.362	1.51 (0.70 – 3.28)	0.295
Glaucoma (n = 601)	1.18 (0.76 – 1.86)	0.459	1.00 (0.58 – 1.70)	0.991
Alzheimer's disease‡ (n = 245)	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Cataracts (n = 2,616)	1.25 (0.94 – 1.67)	0.119	1.34 (1.01 – 1.80)	0.039
AMD (n = 668)	1.83 (1.14 – 2.96)	0.013	1.87 (1.13 – 3.09)	0.014
DR (n = 201)	0.39 (0.05 – 2.79)	0.348	0.46 (0.06 – 3.33)	0.439
Glaucoma (n = 601)	0.93 (0.46 – 1.88)	0.836	0.69 (0.28 – 1.68)	0.410
Vascular dementia§ (n = 213)	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Cataracts (n = 2,616)	1.30 (0.96 – 1.76)	0.084	1.41 (1.02 – 1.95)	0.037
AMD (n = 668)	1.08 (0.59 – 2.01)	0.795	1.25 (0.67 – 2.33)	0.474
DR (n = 201)	2.96 (1.30 – 6.73)	0.010	2.63 (1.10 – 6.27)	0.029
Glaucoma (n = 601)	1.35 (0.71 – 2.56)	0.355	1.12 (0.52 – 2.40)	0.767

AMD = Age-related macular degeneration; DR = Diabetic retinopathy; CI = Confidence interval

*Adjusted for demographics (age, sex, race, years of education); †Adjusted for demographics (age, sex, race, years of education), cardiovascular and dementia risk factors (body mass index, smoking status, alcohol intake, physical activity level, total cholesterol level, diabetes mellitus status, hypertension status, history of cardiovascular disease, history of cerebrovascular disease, and apolipoprotein E ε4 allele), cohort, and clinic site; ‡Alzheimer's disease without VaD using the National Institute of Neurological and Communicative Disorders and Stroke criteria (possible or probable) [57]; §Vascular dementia with or without AD using the Alzheimer's Disease Diagnostic and Treatment Centers criteria (possible or probable) [60]

These results did not change appreciably when excluding participants with MCI (**Table 4.3**).

Table 4.3. Associations between specific ophthalmic conditions (combined model) and risk of all-cause dementia, excluding those with mild cognitive impairment

Outcome and Specific Ophthalmic Condition	Cognitively normal only (n = 2,798)	
All-cause dementia	**Hazard ratio (95% confidence interval)***	**p-value**
Cataracts	1.33 (1.07 – 1.66)	0.011
AMD	1.49 (1.01 – 2.18)	0.042
DR	1.62 (0.75 – 3.50)	0.223
Glaucoma	1.12 (0.65 – 1.91)	0.688
Alzheimer's disease	**Hazard ratio (95% confidence interval)***	**p-value**
Cataracts	1.29 (1.00 – 2.04)	0.047
AMD	1.80 (1.09 – 2.99)	0.023
DR	0.53 (0.07 – 3.86)	0.532
Glaucoma	0.79 (0.32 – 1.92)	0.600
Vascular dementia	**Hazard ratio (95% confidence interval)***	**p-value**
Cataracts	1.39 (1.01 – 1.93)	0.044
AMD	1.22 (0.65 – 2.26)	0.538
DR	2.76 (1.16 – 6.58)	0.022
Glaucoma	1.19 (0.56 – 2.56)	0.647

AMD = Age-related macular degeneration; DR = Diabetic retinopathy

*Adjusted for demographics (age, sex, race, years of education), cardiovascular and dementia risk factors (body mass index, smoking status, alcohol intake, physical activity level, total cholesterol level, diabetes mellitus status, hypertension status, history of cardiovascular disease, history of cerebrovascular disease, and apolipoprotein E ε4 allele), cohort, and clinic site

4.3.2 *Secondary Analyses*

Age, sex, and ApoE genotype modified associations between cataracts and dementia, as well as between AMD and dementia (**Supplemental Tables 4.3-4.5**). Except for an interaction between cataracts and sex ($P = 0.045$), significant statistical interactions were lacking between age, sex, and ApoE genotype and each ophthalmic condition on risk of dementia. Additional covariates included in the primary models, such as income level and access to medical care, refractive errors, inflammatory markers, and treatment for cataracts, glaucoma, or AMD, showed more pronounced results compared to the primary analyses (**Supplemental Table 4.6**). Due to missing data, we conducted multiple imputation for the observed missing data, which showed that the results did not change substantially compared to the primary results from the complete case analysis (**Supplemental Table 4.7**).

4.4 Discussion

The differential associations we found between each ophthalmic condition and dementia have important implications on potential disease pathways shared between the eye and the brain. These findings suggest that the predictive ability of these specific ophthalmic conditions vary by dementia subtype, which reflects different underlying pathologic mechanisms, such as neurodegenerative disease versus vascular disease.

We found that cataracts, which included different types and causes, were associated with a significantly increased risk for all-cause dementia and AD. Based on animal models, including transgenic AD mice, Aβ has been shown to deposit in the crystalline lens, indicating that AD-associated pathologic mechanisms may be related to the development of age-related cataracts [24]. Findings in human lenses, however, have been inconsistent. While some studies have detected Aβ in the lens with a high degree of accuracy, others have not been able to replicate the results using different methods [125,126]. Evidence from population-based studies is limited, with one cohort study finding no association between cataracts and dementia [122]. Given the discrepancies among the published results concerning Aβ signatures in the lens and paucity of epidemiologic evidence, our results add important knowledge in supporting the connection between AD-related changes and the human lens. Our finding of a significant association between cataracts and risk of VaD may be due to inclusion of cases with both VaD and AD in our definition of VaD, but given that the strength of association was higher for VaD than AD, the possibility of a shared vascular pathology is intriguing and would benefit from replication in future studies.

Similar to results for cataracts, we found a significantly increased risk for all-cause dementia and AD associated with AMD. Aβ has been found in drusen among patients with AMD, which are extracellular deposits that are characteristic of this disease [23]. Aβ in drusen may contribute to AMD progression by mediating oxidative stress, uncontrolled inflammation and imbalanced angiogenesis [23], similar to its role in AD. AMD and AD may also share a genetic link through ApoE, in which the ε4 allele is known to increase AD risk. A previous study in CHS found that the ε2 allele was associated with 2.5 times greater odds of late age-related maculopathy, whereas the ε4 allele may confer some protection [108]. Although this pattern is opposite of what is observed in AD, this common genetic connection would be consistent with involvement of ApoE in Aβ proteolysis and neuronal cell membrane renewal in the brain and macula. A meta-analysis found a significant association between AMD and dementia, including AD [127]. Furthermore, other epidemiologic studies suggest that the dry form of AMD is more strongly related to cognitive impairment than the wet form of AMD [128,129]. Differences in dry versus wet AMD may explain the lack of an association with VaD in our study as most cases of AMD are the dry type, which targets the macula, whereas wet AMD represents a smaller proportion of AMD cases and is typified by choroidal neovascularization under the retina [130].

In contrast to the findings with AMD, we observed that DR was associated with a significantly increased risk for VaD, but not AD, though these estimates should be interpreted cautiously as the small number of dementia cases in this group resulted in reduced precision. While diabetes mellitus (DM) has been established to increase risk of dementia, including AD and VaD [131], the association between dementia and DR, which is one of the microvascular complications of DM, is unclear. Some studies have found DR to be associated only with AD [122,132], while other studies have found associations only with VaD [133,134]. In CHS, retinopathy, which included microaneurysms and retinal hemorrhages, was found to be associated with 2.1 times greater odds of dementia among participants with hypertension [135], which share similar effects on structural cerebral microvascular alterations as with diabetes. Aβ has been found in the retinas of patients with DR, but vascular factors, including both micro- and macrovascular disease, also play an important role in AD cerebrovascular pathology [136]. In addition, Aβ influences the cerebral and retinal vasculature through its aggregation and accumulation as Aβ can be found in the walls of retinal blood vessels, which is important to maintaining the blood-retinal barrier, similar to how the integrity of cerebral blood vessels is important to maintaining the blood-brain barrier [126,137]. A recent autopsy study found that DR was significantly associated with increased risk of deep cerebral microinfarcts, but not with any other neuropathology, including AD neuropathologic change [138]. Given that our models for VaD included cases with and without AD, most of which were mixed VaD/AD cases, the results for DR more likely reflect a shared pathophysiology of the retinal and cerebral microvasculature, such as microvascular lesions, rather than a pure AD pathology.

Finally, we did not find evidence of a significantly increased risk of dementia associated with glaucoma. Previous studies found the frequency of glaucoma to be higher in patients with AD or dementia compared to those cognitively normal individuals [139], as well as some epidemiologic studies showing that individuals with glaucoma to be at higher risk for developing dementia [115,120,140], but not all [116,119,141]. Aβ and phosphorylated tau have also been detected in the vitreous of patients with glaucoma, which may lead to axonal loss and neuronal cell death of retinal ganglion cells [23]. However, findings from other studies argue against glaucoma representing a primary neurodegeneration based on features of glaucoma that are not consistent with a neurodegenerative process. These include differences in the specificity of neuronal populations affected in glaucoma and AD, as well as the roles of protein misfolding and intraocular pressure for both conditions [142]. Despite the characteristics that glaucoma shares with neurodegenerative processes, such as AD, several features set glaucoma apart, which should motivate further studies to clarify this complex relationship.

An important implication of our results applies to the potential use of ocular biomarkers for early detection of dementia. Several biomarkers have been proposed to visualize changes in the retina. Measurement of retinal fluorescence in drusen by ultra-wide-field fluorescence imaging and fluorescence lifetime imaging ophthalmoscopy may serve as a biomarker for AD [143]. Retinal Aβ imaging in drusen by spectral imaging may also be used as an AD biomarker, while changes to the retinal vasculature can be measured by fundus photography, as well as by confocal laser scanning microscopy [144,145]. Optical coherence tomography (OCT) angiography is a recent, non-invasive technique also used to visualize the microvasculature of the retina and the choroid [145]. Retinal thickness of the nerve fiber layer, which has been associated with AD progression and degree of cognitive impairment, can be measured by OCT as well [143]. Compared to these possible retinal biomarkers, though, the development of lens biomarkers has not been as robust. A small clinical study used fluorescence imaging to detect Aβ in the lens and predicted the clinical diagnoses of patients with AD with 85% sensitivity and 95% specificity [146]. While the eye holds promise to provide unique insights and opportunities for research and clinical interventions, further studies are needed to validate these potential ocular biomarkers of dementia and develop methods to differentiate AD pathology from other common ophthalmic and systemic diseases.

The large sample and well-characterized CHS data, which also was linked to data from Medicare Part B, are strengths of the study, but several limitations exist. Ophthalmic diagnoses relied on ICD-9 codes and diagnostic criteria for these conditions may have changed over time, which could result in significant variation. However, the extensive longitudinal follow-up in the majority of the cohort reduces the likelihood of this possibility because most participants would have been seen by multiple providers over the course of long-term ophthalmic care. The methods used to ascertain dementia and date of onset in the CHS Cognition Study were nontraditional and may have resulted in misclassification. This type of error would have attenuated our associations toward the null, though, and would not have changed the overall conclusions. Even though participants were followed up for up to nine years, given the long preclinical stage of dementia, which can last for decades before obvious symptoms appear [147], we were unable to clearly establish the temporal sequence between the onset of each ophthalmic condition and development of dementia. Additional research is needed to determine whether these predictors of dementia are also possible risk factors, and if so, to elucidate potential causal pathways, such as mediation by vision loss. Although we adjusted for income and education, as well as access to medical care as proxies for socioeconomic status and availability of medical services, unmeasured or residual confounding may still exist. Finally, the results of this study are relevant only to those who live beyond age 65 years without dementia, and generalizations should be made only to this group.

The ability to evaluate some of the most common ophthalmic conditions among older adults in the CHS cohort provides insight into the connection between the brain and the eye. Cataracts, AMD and DR were independently associated with increased risk of dementia. These associations may reflect different mechanisms between the eye and brain that lead to dementia. As the public health burden of dementia is expected to grow over the next decades, evaluation of the eye in older adults may help identify patients at elevated risk of developing dementia.

Chapter 5. CONCLUSIONS

Our ears and eyes help us to interact with the environment around us, which impacts our health and overall well-being. Studies comprising this dissertation project showed that deficits in hearing and vision in older adults, especially dual sensory impairment (DSI), were associated with increased risk of dementia. We also found that duration and severity of DSI were associated with dementia risk in a graded fashion. In addition to examining associations between sensory impairments and dementia, we looked at specific diagnoses related to visual impairment in older adults and their associations with risk of dementia, including Alzheimer's disease (AD) and vascular dementia (VaD). Cataracts were associated with increased risks for AD and VaD, while age-related macular degeneration (AMD) was associated with increased risk for AD and diabetic retinopathy (DR) was associated with increased risk for VaD.

Previous studies found that a greater number of sensory impairments is associated with increasing risk of dementia in older adults [50]. DSI, in particular, has been associated with cognitive decline and increased risk of cognitive impairment in older adults [25-29]. Results from this dissertation are among the first to show that DSI is associated with significantly increased risk of dementia in older adults, using prospectively collected data from two well-characterized cohorts of older adults focused on the study of cognition and dementia. Findings from the associations between specific ophthalmic conditions and dementia risk in older adults suggest that the relationship between pathologic changes in the eye and the brain may reflect different underlying pathology or pathologies, based on the differential associations observed between each ophthalmic condition and AD dementia versus vascular dementia subtypes, which have not been well-studied previously.

Some strengths of these studies included the prospective, longitudinal design, rigorous ascertainment of dementia in the GEM Study, and longitudinal assessment of hearing and vision in CHS, as well as large sample size in each study. The ability to link CHS data to participants' Medicare records was another key strength to allow for more complete identification of ophthalmic diagnoses. Important limitations, however, include potential misclassification of sensory impairments and ophthalmic diagnoses as hearing and vision were based on self-report and diagnoses of ophthalmic conditions were based on administrative codes, which have not been validated. Ascertainment of dementia subtypes, including AD dementia and VaD, were based on clinical diagnostic criteria, which have limited validity and accuracy, compared with neuropathology-confirmed diagnoses. Overall, findings from this dissertation, which used data from two cohorts well-suited to the study of cognitive function in older adults, provided important and novel evidence that the ears and eyes may serve as predictors of dementia in older adults. The rigorous methods and different approaches, as well as innovative conceptual foundation to study multiple sensory impairments and causes of impairment, to examine associations between hearing and vision, ophthalmic conditions, and dementia risk enhanced what is already known about the impact of these common and age-related conditions on cognitive function in older adults.

These results indicate the importance of getting evaluated for hearing and vision in older adults as sensory impairments or ophthalmic conditions may help to identify older adults who are at elevated risk of developing dementia in the future. In particular, hearing impairment is under-recognized and under-treated, despite its high prevalence and morbidity [8]. Hearing impairment may be under-recognized because it is a slowly developing problem or because of the belief that hearing loss is a normal part of aging. Under-treatment may result from poor appreciation of options for hearing enhancement, or patient resistance or inability to use hearing aids and assistive listening devices. Cost and social stigma are major factors in the diagnosis and management of hearing loss. While current evidence is insufficient for universal eye screening in older adults [148], a comprehensive eye examination every one to two years for all adults 65 years and older is recommended [149]. Following these recommendations can help to identify older adults who are at risk of vision loss, as well as to provide counseling and referrals for disease-specific treatment. Thus, caregivers and providers should facilitate adequate audiologic and ophthalmic care for older adults at risk of dementia.

Additional research is needed to clarify the role of hearing and visual impairments, as well as ophthalmic conditions, on dementia risk. Assuming that diseases of the ocular lens or retina share the same underlying pathologies, such as AD or vascular disease, as dementia, new, non-invasive approaches to early detection of dementia may be possible. Potential ocular biomarkers include measurement of the choroid and retinal microvasculature and thickness of the nerve fiber layer using optical coherence tomography [143,145]. Spectral imaging may also be used to image retinal β-amyloid (Aβ) in drusen [144,145], while fluorescence imaging has been used to detect Aβ in the lens [146]. Ophthalmic conditions may also play a causal role in the development of dementia through vision loss. If true, and assuming that vision loss is also a causal factor in the development of dementia, interventions to restore vision, such as cataract surgery [105], may modify the risk of dementia. Interventions to restore hearing among those with hearing loss, such as hearing aids, may also serve to reduce risk or delay dementia onset [104,150], but more studies are necessary to tease apart the interplay of neurodegeneration, cognitive decline, and hearing loss [107]. Hearing loss was identified to have the highest population attributable fraction (8%) among 12 potentially modifiable risk factors for dementia in the most recent *Lancet* Commission [151], so evidence from rigorously conducted observational studies and clinical trials will be important to evaluate the effect of hearing interventions on the incidence of dementia. Finally, an important area of research for individuals with DSI is to develop devices that improve usability for those with DSI as most assistive technology rely on the use of the unimpaired sense in either vision or hearing [100]. For example, hearing aids are often small and are difficult to see and handle for many older individuals, particularly if they have concurrent visual impairment. Effective strategies to reduce cognitive decline and risk of dementia among older adults with DSI will require careful consideration of the needs and limitations of the patient in order to implement effective rehabilitation practices.

With an aging population, the burden of age-related conditions, such as hearing and vision loss and ophthalmic conditions is expected to increase over time, impacting patients and their families, as well as putting additional pressures on health care systems and economic policies. Dementia is a major public health challenge that, despite massive investments in developing effective treatments, will require a risk reduction, prevention-oriented approach to stem the number of new cases over the next decades. The connections between the ears and eyes with the brain, as discussed in this dissertation, provide some promise that evaluation of hearing and vision can help with less invasive, less costly, and more accessible and scalable methods of early detection, and ultimately, prevention of dementia.

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SUPPLEMENTAL DATA

Supplemental Table 2.1. Associations between total number of sensory impairments and risk of all-cause dementia stratified by age, sex, and ApoE

	Age†					
	<80 years (n = 1,406)		**80-84 years (n = 538)**		**≥85 years (n = 107)**	
Number of sensory impairments	**Hazard Ratio (95% CI)***	**p-value**	**Hazard Ratio (95% CI)***	**p-value**	**Hazard Ratio (95% CI)***	**p-value**
No sensory impairment	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Single sensory impairment	1.28 (0.91 – 1.80)	0.16	0.99 (0.64 – 1.54)	0.97	0.89 (0.28 – 2.80)	0.84
Dual sensory impairment	1.73 (0.96 – 3.12)	0.07	1.85 (0.94 – 3.67)	0.08	3.90 (0.99 – 15.3)	0.05

	Sex†			
	Female (n = 904)		**Male (n = 1,146)**	
Number of sensory impairments	**Hazard Ratio (95% CI) ***	**p-value**	**Hazard Ratio (95% CI) ***	**p-value**
No sensory impairment	1.00 (Reference)		1.00 (Reference)	
Single sensory impairment	1.32 (0.92 – 1.89)	0.13	0.92 (0.63 – 1.35)	0.67
Dual sensory impairment	2.21 (1.21 – 4.06)	0.01	1.55 (0.91 – 2.64)	0.11

	ApoE genotype†			
	No ε4 allele (n = 1,563)		**≥1 ε4 allele (n = 488)**	
Number of sensory impairments	**Hazard Ratio (95% CI) ***	**p-value**	**Hazard Ratio (95% CI) ***	**p-value**
No sensory impairment	1.00 (Reference)		1.00 (Reference)	
Single sensory impairment	1.16 (0.83 – 1.62)	0.38	1.01 (0.66 – 1.56)	0.96
Dual sensory impairment	2.21 (1.37 – 3.56)	0.001	1.41 (0.67 – 2.99)	0.37

CI = Confidence Interval; ApoE = Apolipoprotein E

*Excluding stratification variable, models adjusted for same covariates as primary model, which include age, sex, race, education, income, body mass index, alcohol intake, smoking status, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, clinic site, treatment status, and ApoE.

†$P_{\text{interaction}} > 0.05$

Supplemental Table 2.2. Associations between total number of sensory impairments and risk of all-cause dementia stratified by mild cognitive impairment (MCI)

	Cognitively normal (n = 1,770)		**Mild cognitive impairment (n = 281)**	
Number of sensory impairments	**Hazard Ratio (95% CI)***	**p-value**	**Hazard Ratio (95% CI)***	**p-value**
No sensory impairment	1.00 (Reference)		1.00 (Reference)	
Single sensory impairment	1.14 (0.83 – 1.57)	0.43	0.81 (0.51 – 1.29)	0.38
Dual sensory impairment	2.08 (1.29 – 3.37)	0.003	1.22 (0.57 – 2.62)	0.61

$P_{interaction} < 0.0001$; CI = Confidence Interval

*Models adjusted for age, sex, race, education, income, body mass index, alcohol consumption, smoking status, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, clinic site, treatment status, and ApoE.

Supplemental Table 2.3. Associations between total number of sensory impairments at baseline and risk of probable Alzheimer's disease

Number of sensory impairments	Hazard Ratio (95% Confidence Interval)*	p-value
No sensory impairment	1.00 (Reference)	
Single sensory impairment	1.09 (0.81 – 1.46)	0.58
Dual sensory impairment	1.97 (1.27 – 3.06)	0.002
Test for trend		0.01

*Model adjusted for age, sex, race, education, income, body mass index, alcohol intake, smoking status, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, clinic site, treatment status, and ApoE.

Supplemental Table 2.4. Competing risk analyses

	All-cause dementia[†]		Alzheimer's disease[‡]		Vascular dementia[§]	
Number of Sensory Impairments	**Hazard Ratio (95% CI)***	**p-value**	**Hazard Ratio (95% CI)***	**p-value**	**Hazard Ratio (95% CI)***	**p-value**
No sensory impairment	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Single sensory impairment	1.10 (0.85 – 1.43)	0.47	1.10 (0.80 – 1.51)	0.57	1.18 (0.72 – 1.94)	0.51
Dual sensory impairment	1.99 (1.34 – 2.96)	0.001	2.19 (1.37 – 3.52)	0.001	1.13 (0.46 – 2.78)	0.78
Test for trend		0.007		0.01		0.56

CI = Confidence interval

[†]Competing event is death; [‡]Competing event is non-Alzheimer's disease; [§]Competing event is non-vascular dementia; *Models adjusted for age, sex, race, education, income, body mass index, alcohol intake, smoking status, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, clinic site, treatment status, and ApoE.

Supplemental Table 2.5. Comparison of results from primary complete case analysis and multiple imputation with chained equations

	All-cause dementia				**Alzheimer's disease**				**Vascular dementia**			
	Complete case analysis		**MICE with 20 imputations***		**Complete case analysis**		**MICE with 20 imputations***		**Complete case analysis**		**MICE with 20 imputations***	
Number of sensory impairments	Coefficient (95% CI)	p	Coefficient (95% CI)	p	Coefficient (95% CI)	p	Coefficient (95% CI)	p	Coefficient (95% CI)	p	Coefficient (95% CI)	p
No sensory impairment	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)		0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
Single sensory impairment	0.11 (-0.16 – 0.37)	0.43	0.17 (-0.03 – 0.38)	0.10	0.09 (-0.23 – 0.41)	0.58	0.23 (-0.02 – 0.48)	0.07	0.18 (-0.31 – 0.67)	0.48	0.03 (-0.37 – 0.44)	0.87
Dual sensory impairment	0.62 (0.22 – 1.02)	<0.01	0.36 (0.02 – 0.70)	0.04	0.75 (0.30 – 1.21)	<0.01	0.41 (-0.02 – 0.83)	0.06	0.20 (-0.66 – 1.06)	0.65	0.09 (-0.59 – 0.76)	0.80
Test for trend		<0.01		0.01		0.01		0.02		0.46		0.78

MICE = Multiple imputation with chained equations; CI = Confidence interval; p = p-value

*Number of imputed values for each variable is as follows: (1) ApoE genotype, N = 617; (2) Hearing or visual impairment, N = 242; (3) Cerebrovascular disease, N = 104; (4) Cardiovascular disease, N = 76; (5) Smoking status, N = 58; (6) Alcohol intake, N = 48; (7) Diabetes, N = 42; (8) Physical activity, N = 33; (9) Income, N = 14; and (10) Body mass index, N = 12. The imputation model included all covariates in the final model.

Supplemental Table 3.1. Self-reported questions on hearing and vision in the Cardiovascular Health Study

Sensory domain	Questions
Hearing	• Can you hear well enough (with hearing aid if necessary) to use the telephone? • Can you hear well enough (with hearing aid if necessary) to listen to a radio? • Can you hear well enough (with hearing aid if necessary) to carry on a conversation?
Vision	• Can you see well enough (with glasses if needed) to drive? • Can you see well enough (with glasses if needed) to watch TV? • Can you see well enough (with glasses if needed) to recognize someone across the room? • Can you see well enough (with glasses if needed) to read the newspaper?

Supplemental Table 3.2. Associations between number of sensory impairments (0, 1, or 2) and dementia only among cognitively normal participants

Participants without Mild Cognitive Impairment (n = 2,515)						
	All-cause dementia		**Alzheimer's disease**		**Vascular dementia**	
Number of Sensory Impairments	**Hazard Ratio (95% CI)***	***P*-value**	**Hazard Ratio (95% CI)***	***P*-value**	**Hazard Ratio (95% CI)***	***P*-value**
No sensory impairment	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Single sensory impairment	1.71 (1.33 – 2.20)	<.001	2.37 (1.66 – 3.37)	<.001	1.36 (0.93 – 1.98)	.11
Dual sensory impairment	2.26 (1.44 – 3.54)	<.001	3.09 (1.70 – 5.61)	<.001	1.82 (0.90 – 3.69)	.10
Test for trend		<.001		<.001		.04

CI = Confidence Interval; *Models adjusted for age, sex, race, education, body mass index, alcohol intake, smoking status, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, total cholesterol, cohort, clinic site, and ApoE.

Supplemental Table 3.3. Comparison of results from primary complete case analysis and multiple imputation with chained equations

	All-cause dementia				**Alzheimer's disease**				**Vascular dementia**			
	Complete case analysis		**MICE with 20 imputations***		**Complete case analysis**		**MICE with 20 imputations***		**Complete case analysis**		**MICE with 20 imputations***	
Number of sensory impairments	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
No sensory impairment	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Single sensory impairment	1.72 (1.34 – 2.21)	<.01	1.72 (1.38 – 2.16)	<.01	2.32 (1.63 – 3.29)	<.01	2.18 (1.60 – 2.97)	<.01	1.38 (0.95 – 2.01)	.09	1.43 (1.02 – 2.01)	.04
Dual sensory impairment	2.60 (1.66 – 4.06)	<.01	2.72 (1.86 – 4.01)	<.01	3.67 (2.03 – 6.60)	<.01	3.39 (2.01 – 5.70)	<.01	2.03 (1.00 – 4.09)	.05	2.48 (1.40 – 4.44)	<.01
Test for trend		<.01		<.01		<.01		<.01		.02		<.01

MICE = Multiple imputation with chained equations; CI = Confidence interval; *Number of imputed values for each variable is as follows: (1) ApoE genotype, N = 239; (2) Diabetes, N = 21; (3) Total cholesterol, N = 16; (4) Hypertension, N = 16 ; (5) Smoking status, N = 10; and (6) Alcohol intake, N = 10. The imputation model included all covariates in the final model.

Supplemental Table 3.4. Associations between number of sensory impairments (0, 1, or 2) and risk of all-cause dementia stratified by age, sex, and ApoE genotype

	Age†			
	<75 years (n = 1,666)		**≥75 years (n = 1,261)**	
Number of sensory impairments	**Hazard Ratio (95% CI)***	***P*-value**	**Hazard Ratio (95% CI)***	***P*-value**
No sensory impairment	1.00 (Reference)		1.00 (Reference)	
Single sensory impairment	1.47 (0.90 – 2.41)	.12	2.01 (1.51 – 2.68)	<.001
Dual sensory impairment	4.41 (2.06 – 9.42)	<.001	2.48 (1.43 – 4.30)	.001
	Sex‡			
	Female (n = 1,704)		**Male (n = 1,223)**	
Number of sensory impairments	**Hazard Ratio (95% CI)***	***P*-value**	**Hazard Ratio (95% CI)***	***P*-value**
No sensory impairment	1.00 (Reference)		1.00 (Reference)	
Single sensory impairment	1.76 (1.27 – 2.44)	.001	1.66 (1.11 – 2.47)	.01
Dual sensory impairment	2.36 (1.34 – 4.14)	.003	2.72 (1.29 – 5.75)	.009
	ApoE genotype§			
	No ε4 allele (n = 2,051)		**≥1 ε4 allele (n = 637)**	
Number of sensory impairments	**Hazard Ratio (95% CI)***	***P*-value**	**Hazard Ratio (95% CI)***	***P*-value**
No sensory impairment	1.00 (Reference)		1.00 (Reference)	
Single sensory impairment	2.01 (1.48 – 2.72)	<.001	1.16 (0.73 – 1.84)	.53
Dual sensory impairment	3.15 (1.82 – 5.42)	<.001	1.84 (0.82 – 4.14)	.14

CI = Confidence Interval; ApoE = Apolipoprotein E; *Excluding stratification variable, models adjusted for same covariates as primary model, which include age, sex, race, education, body mass index, alcohol intake, smoking status, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, total cholesterol, cohort, clinic site, and ApoE; †$P_{interaction}$ <.001; ‡$P_{interaction}$ = .54; §$P_{interaction}$ = .02.

Supplemental Table 4.1. Diagnostic and procedure codes for selected ophthalmic conditions

Ophthalmic Condition	ICD-9 Code(s)	CPT Code(s)
Age-related macular degeneration	362.50, 362.51, 362.52	67028, 67043
Cataracts	366.*	66982, 66984
Diabetic retinopathy	362.0*	67028, 67113, 67042
Glaucoma	365.* (except 365.0*)	65855, 66150, 66155, 66160, 66170, 66172, 66174, 66175, 66179, 66180, 66183, 66184, 66185, 66625, 66630, 66635, 66700, 66710, 66711, 66720, 0191T, 0235T, 0376T, 0449T, 0450T, 0474T
Uncorrected refractive errors		
Astigmatism	367.0	
Hypermetropia	367.1	
Myopia	367.2*	
Presbyopia	367.4	

ICD-9 = International Classification of Diseases, Ninth Revision; CPT = Current Procedural Terminology

Supplemental Table 4.2. Demographic and baseline clinical factors by ophthalmic condition status at end of follow-up in the CHS Cognition Study

Baseline factors*	**Overall (n = 3,375)**	**No diagnosis of ≥1 ophthalmic condition (cataract, AMD, DR, glaucoma) by end of study period (n = 571)**	**Diagnosis of ≥1 ophthalmic condition (cataract, AMD, DR, glaucoma) by end of study period (n = 2,804)**
Age[†], mean (SD), years	74.8 (4.9)	74.4 (4.9)	74.9 (4.9)
Sex, No. (%)			
Female	1,977 (58.6)	327 (57.3)	1,650 (58.8)
Male	1,398 (41.4)	244 (42.7)	1,154 (41.2)
Race, No. (%)			
White	2,867 (85.0)	410 (71.8)	2,457 (87.6)
Nonwhite	508 (15.0)	161 (28.2)	347 (12.4)
Education, No. (%)			
Less than high school	810 (24.0)	146 (25.6)	664 (23.7)
High school graduate	966 (28.7)	181 (31.8)	785 (28.0)
Some college	808 (24.0)	126 (22.1)	682 (24.3)
College graduate	786 (23.3)	117 (20.5)	669 (23.9)
Smoking status, No. (%)			
Never	1,605 (47.6)	258 (45.2)	1,347 (48.0)
Former	1,401 (41.6)	232 (40.6)	1,169 (41.7)
Current	365 (10.8)	81 (14.2)	284 (10.1)
Alcohol intake, mean (SD), drinks/week	2.8 (12.6)	3.0 (7.6)	2.8 (13.4)
Body mass index, mean (SD), kg/m^2	26.5 (4.4)	26.7 (4.2)	26.5 (4.4)
Physical activity, No. (%)			
No exercise	208 (6.2)	32 (5.6)	176 (6.3)
Low exercise	1,512 (44.8)	254 (44.5)	1,258 (44.9)
Moderate exercise	1,252 (37.1)	226 (39.6)	1,026 (36.6)
High exercise	401 (11.9)	59 (10.3)	342 (12.2)
Diabetes mellitus, No. (%)			

Normal	2,471 (73.8)	401 (70.7)	2,070 (73.8)
Impaired fasting glucose	439 (13.1)	88 (15.5)	351 (12.5)
Diabetes mellitus	440 (13.1)	78 (13.8)	362 (12.9)
Hypertension, No. (%)			
Normal	1,515 (44.9)	234 (41.0)	1,281 (45.7)
Borderline	479 (14.2)	101 (17.7)	378 (13.5)
Hypertensive	1,378 (40.9)	236 (41.3)	1,142 (40.7)
Cardiovascular disease[‡], No. (%)			
Yes	569 (16.9)	99 (17.3)	470 (16.8)
No	2,806 (83.1)	472 (82.7)	2,334 (83.2)
Cerebrovascular disease[§], No. (%)			
Yes	142 (4.2)	29 (5.1)	113 (4.0)
No	3,233 (95.8)	542 (94.9)	2,691 (96.0)
Total cholesterol[¶], mean (SD), mg/dL	211.4 (38.2)	210.4 (39.3)	211.6 (38.0)
ApoE genotype, No. (%)			
Presence of ε4 allele	746 (22.1)	140 (24.5)	606 (21.6)
No ε4 allele	2,343 (69.4)	384 (67.2)	1,959 (69.9)

AMD = Age-related macular degeneration; ApoE = Apolipoprotein E; DR = Diabetic retinopathy; SD = Standard deviation; kg/m^2 = kilograms per meter squared; mg/dL = milligrams per deciliter

*Information was collected around the time of the cranial MRI between 1992 and 1994, and was missing for some variables as follows: Education: n = 4 (0.1%) among those who developed an ophthalmic condition, n = 1 (0.2%) among those who did not develop an ophthalmic condition; Smoking status: n = 4 (0.1%) among those who developed an ophthalmic condition, n = 0 (0%) among those who did not develop an ophthalmic condition; Alcohol intake: n = 9 (0.3%) among those who developed an ophthalmic condition, n = 4 (0.7%) among those who did not develop an ophthalmic condition; Body mass index: n = 5 (0.2%) among those who developed an ophthalmic condition, n = 4 (0.7%) among those who did not develop an ophthalmic condition; Physical activity: n = 2 (0.1%) among those who developed an ophthalmic condition, n = 0 (0%) among those who did not develop an ophthalmic condition; Diabetes mellitus: n = 21 (0.7%) among those who developed an ophthalmic condition, n = 4

(0.7%) among those who did not develop an ophthalmic condition; Hypertension: n = 3 (0.1%) among those who developed an ophthalmic condition, n = 0 (0%) among those who did not develop an ophthalmic condition; Total cholesterol: n = 18 (0.6%) among those who developed an ophthalmic condition, n = 2 (0.4%) among those who did not develop an ophthalmic condition; ApoE genotype: n = 239 (8.5%) among those who developed an ophthalmic condition, n = 47 (8.2%) among those who did not develop an ophthalmic condition; †Age = Age at MRI; ‡Cardiovascular disease defined as prevalent angina, congestive heart failure, coronary heart disease, claudication, or myocardial infarction at baseline; §Cerebrovascular disease defined as prevalent stroke or transient ischemic attack at baseline; ¶To convert total cholesterol from milligrams per deciliter to millimoles per liter, multiply by 0.0259.

Supplemental Table 4.3. Associations between specific ophthalmic conditions (combined model) and risk of all-cause dementia, stratified by age

Age (<80 years vs. ≥80 years)					
	<80 years (n = 2,781)		≥80 years (n = 594)		
Ophthalmic condition	**Hazard Ratio (95% CI)***	**p-value**	**Hazard Ratio (95% CI)***	**p-value**	**$p_{interaction}$†**
Cataracts	1.21 (0.91 – 1.61)	0.181	1.79 (1.24 – 2.58)	0.002	0.513
AMD	1.90 (1.15 – 3.14)	0.012	1.25 (0.69 – 2.26)	0.455	0.440
DR	1.62 (0.64 – 4.07)	0.309	1.31 (0.30 – 5.70)	0.717	0.177
Glaucoma	0.69 (0.31 – 1.57)	0.382	1.50 (0.73 – 3.11)	0.271	0.738

AMD = Age-related macular degeneration; DR = Diabetic retinopathy; CI = Confidence interval

*Adjusted for demographics (age, sex, race, years of education), cohort, clinic site, cardiovascular and dementia risk factors (body mass index, smoking status, alcohol intake, physical activity level, total cholesterol level, diabetes mellitus status, hypertension status, history of cardiovascular disease, history of cerebrovascular disease, and apolipoprotein E ε4 allele); †Age as a continuous variable (years)

Supplemental Table 4.4. Associations between specific ophthalmic conditions (combined model) and risk of all-cause dementia, stratified by sex

Sex (Female vs. Male)					
	Females (n = 1,977)		**Males (n = 1,398)**		
Ophthalmic condition	**Hazard Ratio (95% CI)***	**p-value**	**Hazard Ratio (95% CI)***	**p-value**	$p_{interaction}$
Cataracts	1.66 (1.24 – 2.20)	0.001	1.04 (0.73 – 1.49)	0.823	0.045
AMD	1.75 (1.08 – 2.84)	0.024	1.34 (0.72 – 1.64)	0.361	0.533
DR	1.52 (0.54 – 4.23)	0.427	1.58 (0.48 – 5.18)	0.454	0.870
Glaucoma	0.95 (0.47 – 1.95)	0.898	1.06 (0.46 – 2.41)	0.898	0.906

AMD = Age-related macular degeneration; DR = Diabetic retinopathy; CI = Confidence interval

*Adjusted for demographics (age, race, years of education), cohort, clinic site, cardiovascular and dementia risk factors (body mass index, smoking status, alcohol intake, physical activity level, total cholesterol level, diabetes mellitus status, hypertension status, history of cardiovascular disease, history of cerebrovascular disease, and apolipoprotein E ε4 allele)

Supplemental Table 4.5. Associations between specific ophthalmic conditions (combined model) and risk of all-cause dementia, stratified by ApoE genotype

ApoE genotype (0 ε4 allele vs. ≥1 ε4 allele)					
	No ε4 allele (n = 2,343)		≥1 ε4 allele (n = 746)		
Ophthalmic condition	**Hazard Ratio (95% CI)***	**p-value**	**Hazard Ratio (95% CI)***	**p-value**	$p_{interaction}$
Cataracts	1.48 (1.13 – 1.95)	0.004	1.17 (0.80 – 1.72)	0.411	0.343
AMD	1.70 (1.08 – 2.69)	0.023	1.36 (0.67 – 2.73)	0.395	0.459
DR	1.55 (0.61 – 3.89)	0.355	1.34 (0.32 – 5.73)	0.689	0.869
Glaucoma	1.09 (0.59 – 2.02)	0.772	0.74 (0.23 – 2.37)	0.618	0.595

AMD = Age-related macular degeneration; DR = Diabetic retinopathy; CI = Confidence interval

*Adjusted for demographics (age, sex, race, years of education), cohort, clinic site, cardiovascular and dementia risk factors (body mass index, smoking status, alcohol intake, physical activity level, total cholesterol level, diabetes mellitus status, hypertension status, history of cardiovascular disease, and history of cerebrovascular disease)

Supplemental Table 4.6. Risk of all-cause dementia, Alzheimer's disease, and vascular dementia associated with specific ophthalmic conditions, adjusted for income and healthcare access, refractive errors, inflammatory markers, and eye treatments/procedures

Outcome and Specific Ophthalmic Condition	Model 3*		Model 4†		Model 5‡		Model 6§	
All-cause dementia	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Cataracts	1.61 (1.25 – 2.08)	<0.001	1.70 (1.33 – 2.19)	<0.001	1.53 (1.19 – 1.96)	0.001	1.67 (1.32 – 2.12)	<0.001
AMD	1.81 (1.17 – 2.81)	0.008	2.16 (1.43 – 3.26)	<0.001	1.89 (1.24 – 2.89)	0.003	2.27 (1.51 – 3.41)	<0.001
DR	1.94 (0.88 – 4.28)	0.098	2.02 (0.92 – 4.44)	0.080	1.96 (0.89 – 4.31)	0.094	2.34 (1.06 – 5.14)	0.035
Glaucoma	1.24 (0.66 – 2.30)	0.504	1.41 (0.80 – 2.46)	0.232	1.20 (0.66 – 2.18)	0.545	1.59 (0.91 – 2.77)	0.105
Alzheimer's disease	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Cataracts	1.59 (1.12 – 2.26)	0.009	1.71 (1.19 – 2.45)	0.003	1.53 (1.08 – 2.17)	0.018	1.62 (1.16 – 2.27)	0.005
AMD	2.16 (1.23 – 3.80)	0.007	2.58 (1.50 – 4.47)	0.001	2.12 (1.21 – 3.73)	0.009	2.59 (1.52 – 4.440	0.001
DR	0.54 (0.07 – 3.99)	0.548	0.62 (0.08 – 4.60)	0.644	0.60 (0.08 – 4.45)	0.621	0.69 (0.09 – 5.08)	0.716
Glaucoma	0.64 (0.20 – 2.04)	0.448	1.00 (0.40 – 2.50)	0.993	0.94 (0.37 – 2.33)	0.886	1.07 (0.43 – 2.68)	0.883
Vascular dementia	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Cataracts	1.66 (1.14 – 2.43)	0.008	1.65 (1.14 – 2.38)	0.007	1.48 (1.02 – 2.15)	0.040	1.69 (1.18 – 2.41)	0.004
AMD	1.53 (0.75 – 3.14)	0.246	1.67 (0.86 – 3.23)	0.126	1.56 (0.79 – 3.10)	0.200	1.88 (0.98 – 3.62)	0.059
DR	3.68 (1.50 – 9.03)	0.004	3.33 (1.36 – 8.14)	0.008	3.34 (1.36 – 8.19)	0.008	4.02 (1.64 – 9.85)	0.002

Glaucoma	1.87 (0.84 – 4.15)	0.123	1.51 (0.68 – 3.34)	0.309	1.13 (0.45 – 2.82)	0.799	1.80 (0.81 – 3.97)	0.146

AMD = Age-related macular degeneration; DR = Diabetic retinopathy; CI = Confidence interval

*Adjusted for same set of covariates as in Model 2 + income and access to medical care. Income was based on self-reported total combined family income, before taxes, for the past 12 months. Income groups were categorized as: (1) Under $5,000; (2) $5,000 to $7,999; (3) $8,000 to $11,999; (4) $12,000 to $15,999; (5) $16,000 to $24,999; (6) $25,000 to $34,999; (7) $35,000 to $49,999; and (8) Over $50,000. Access to medical care was based on self-reported answers to whether the participant's ability to see a doctor in the past year was affected by the following: (1) Not having a regular doctor; (2) Taking care of others; (3) Difficulty finding transportation; (4) Doctor/Clinic/Hospital bills; and (5) Work responsibilities; †Adjusted for same set of covariates as in Model 2 + diagnosis of refractive errors (presbyopia, astigmatism, hypermetropia, and myopia); ‡Adjusted for same set of covariates as in Model 2 + inflammatory markers (C-reactive protein level and interleukin-6 level); §Adjusted for same set of covariates as in Model 2 + treatment for cataracts, AMD, DR, or glaucoma.

Supplemental Table 4.7. Comparison of results from primary complete case analysis and multiple imputation with chained equations

	All-cause dementia				Alzheimer's disease				Vascular dementia			
	Complete case analysis		MICE with 20 imputations*		Complete case analysis		MICE with 20 imputations*		Complete case analysis		MICE with 20 imputations*	
Specific ophthalmic condition	Coefficient† (95% CI)	p	Coefficient† (95% CI)	p	Coefficient† (95% CI)	p	Coefficient† (95% CI)	p	Coefficient† (95% CI)	p	Coefficient† (95% CI)	p
Cataracts	0.44 (0.20 – 0.68)	<0.01	0.37 (0.15 – 0.59)	<0.01	0.39 (0.06 – 0.72)	0.02	0.35 (0.04 – 0.66)	0.03	0.48 (0.12 – 0.83)	<0.01	0.40 (0.08 – 0.73)	0.02
AMD	0.67 (0.27 – 1.08)	<0.01	0.58 (0.19 – 0.96)	<0.01	0.79 (0.26 – 1.32)	<0.01	0.71 (0.20 – 1.22)	<0.01	0.49 (-0.16 – 1.14)	0.14	0.36 (-0.28 – 1.00)	0.28
DR	0.62 (-0.16 – 1.40)	0.12	0.43 (-0.35 – 1.20)	0.28	-0.60 (-2.60 – 1.39)	0.55	-0.80 (-2.78 – 1.19)	0.43	1.18 (0.29 – 2.07)	0.01	1.03 (0.15 – 1.90)	0.02
Glaucoma	0.25 (-0.30 – 0.80)	0.38	0.40 (-0.06 – 0.87)	0.09	-0.15 (-1.06 – 0.76)	0.74	0.13 (-0.60 – 0.86)	0.72	0.39 (-0.40 – 1.18)	0.33	0.58 (-0.09 – 1.24)	0.09

AMD = Age-related macular degeneration; DR = Diabetic retinopathy; MICE = Multiple imputation with chained equations; CI = Confidence interval; p = p-value

*Number of imputed values for each variable is as follows: (1) ApoE genotype, N = 676; (2) Diabetes, N = 55; (3) Total cholesterol, N = 41; (4) Alcohol intake, N = 25; (5) Body mass index, N = 18; (6) Education, N = 16; (7) Hypertension, N = 6; (8) Smoking status, N = 6; and (9) Physical activity, N = 5. The imputation model included all covariates in the final model; †Coefficient = log(Hazard Ratio)

VITA

Phillip Hwang is a native to the Pacific Northwest, born in Anchorage, Alaska, and raised in Seattle, Washington. He attended Brown University as an undergraduate student and then Columbia University as a graduate student. After completion of his PhD, Phillip will be at Boston University for a post-doctoral fellowship where he will continue his training to be an independent researcher in Alzheimer's disease and dementia.