

The Association between Vision Impairment and Incidence of Dementia and Cognitive Impairment

A Systematic Review and Meta-analysis

Xianwen Shang, MPH, PhD,¹ Zhuoting Zhu, MD, PhD,¹ Wei Wang, MD, PhD,² Jason Ha, MBBS, BMedSc,³ Mingguang He, MD, PhD^{1,2,3}

Topic: The magnitude and direction of the association between vision impairment and incident dementia and cognitive impairment in prospective cohort studies was estimated by systematic review and meta-analysis. The global burden of dementia associated with vision impairment then was estimated.

Clinical Relevance: Because a predominant proportion of vision impairment is preventable or treatable, investigating its association with dementia may help to identify an important modifiable factor for the prevention of dementia.

Methods: A literature search was conducted using PubMed, Embase, Web of Science, and Google Scholar on September 15, 2020. Relative risks (RRs) were pooled using random-effects models and stratified analyses for subgroups representing different study characteristics. Publication bias was evaluated with funnel plots and the Egger test. The global burden of dementia associated with vision impairment was estimated based on the Global Burden of Disease Study data on the prevalence of dementia and vision impairment.

Results: In the meta-analysis of 14 prospective cohort studies with 6 204 827 participants and 171 888 dementia patients, the pooled RR associated with vision impairment was 1.47 (95% confidence interval [CI], 1.36–1.60). In the meta-analysis of 12 prospective cohort studies with 45 313 participants and 13 350 patients with cognitive impairment, the pooled RR was 1.35 (95% CI, 1.28–1.41). Stratified analyses showed that the associations of vision impairment with incident dementia and cognitive impairment were similar across methods of vision assessment, length of follow-up, and study quality. The global number of people with dementia associated with moderate or severe vision impairment in 2016 was 2.1 million (80% uncertainty interval, 1.0–3.3 million), which accounted for 4.7% (95% CI, 2.3%–7.5%) of the global burden of dementia. Economic inequality was significant for the burden of dementia associated with vision impairment.

Discussion: The overall quality of the body evidence was low because of the observational design of the studies included in the analysis. Vision impairment is associated with an increased risk of both dementia and cognitive impairment in older adults. Screening and treating vision impairment, especially in low- and middle-income countries, may help to alleviate the global burden of dementia. *Ophthalmology* 2021;128:1135–1149 © 2021 by the American Academy of Ophthalmology



Supplemental material available at www.aaojournal.org.

In 2016, dementia was the fifth leading cause of death globally, accounting for 2.4 million deaths.¹ The global number of people living with dementia was 43.8 million in 2016¹ and is estimated to reach 152 million by 2050.² Since 2010, the economic burden of dementia has increased by 35% to \$818 billion United States dollars in 2015 and is projected to rise to approximately \$2 trillion United States dollars in 2030.³ Its significant mortality and morbidity represent a tremendous burden on health care and economic systems globally. Because mild cognitive impairment may precede the onset of more severe functional impairment by many years,⁴ a potential

preventative window exists during which the onset of clinical dementia may be delayed. Therefore, it is imperative to identify important modifiable risk factors amenable to intervention for the prevention of dementia and cognitive decline in a rapidly ageing global population.^{5,6}

Sensory impairment plays an important role in the development of dementia, with hearing loss in midlife identified as the leading risk factor of dementia globally.⁶ Vision as another form of the sensory stimulus also warrants scrutiny, given that a large proportion of vision impairment (80.0% in 2020) is preventable or treatable.⁷

Longitudinal studies have shown that vision impairment is associated with accelerated cognitive decline,^{8–14} and causes of vision impairment such as age-related macular degeneration and glaucoma also are linked to Alzheimer's disease.^{15,16} However, until 2016, only 1 prospective study had linked vision impairment to dementia. Since 2017, a growing number of prospective cohort studies have investigated the association of vision impairment with dementia, cognitive impairment, or both, but the results have been far from consistent.^{17–20} For example, a recent longitudinal study of 1061 women 66 to 84 years of age at baseline found that those with vision impairment at baseline were more than twice as likely to demonstrate dementia over 4 years than those without vision impairment.¹⁷ In contrast, another longitudinal analysis of 1810 Black and White participants from the Health, Aging, and Body Composition Study 70 to 79 years of age at baseline reported that vision impairment was not associated significantly with incident dementia over 10 years (hazard ratio [HR], 1.26; 95% confidence [CI], 0.90–1.77).²¹

However, no published systematic reviews and meta-analyses have been conducted on this topic. With no known cure or treatment for dementia presently, it is imperative to identify a modifiable risk factor implicated in the development of dementia that may be a potential preventive target. Therefore, it is of great importance to perform a meta-analysis to summarize the direction and magnitude of the association between vision impairment and both incident dementia and cognitive impairment in prospective studies. The global burden of dementia associated with 12 modifiable risk factors (low education, hearing loss, traumatic brain injury, excessive alcohol consumption, obesity, hypertension, smoking, depression, diabetes, social isolation, physical inactivity, and air pollution) has been estimated by the 2020 report of the Lancet Dementia Commission.⁶ Also, investigators have significant interest in the estimation of other important modifiable risk factors such as vision impairment if vision impairment can be demonstrated to be associated with an increased risk of dementia in our meta-analysis.

A systematic review and meta-analysis of the recently published prospective cohort studies was conducted to determine whether vision impairment was a predictor for the development of dementia and cognitive decline. The magnitude of this association and the global burden of dementia associated with vision impairment also were analyzed.

Methods

Eligibility Criteria

We conducted a systematic review and meta-analysis according to the Systematic Reviews and Meta-analyses Guidelines.²² This study is registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (identifier, CRD42020198341). All prospective cohort studies reporting the association between vision impairment and dementia or cognitive impairment were included in the systematic review. The criteria for inclusion of studies in our meta-analysis included prospective

design; quality score of more than 5; end points of dementia, Alzheimer's disease, or cognitive impairment; presentation of quantitative point estimates (HRs, relative risks [RRs], or odds ratios) and variance of the estimates of the association between vision impairment and outcomes; and description of adjustment for potential confounders. Study quality was assessed independently by 2 members of the research team (X.S. and Z.Z.) using the Newcastle-Ottawa Scale,²³ which is the most frequently used quality tool for cohort studies.²⁴ With regard to duplicate reports from the same study, the most recent publication or the publication with the largest sample size was selected.

The primary and secondary outcomes were incident dementia and cognitive impairment during follow-up, respectively. Dementia is a neurocognitive disorder that is associated with a significant functional deficit in language, behavior, and cognition,²⁵ whereas cognitive impairment is the prelude to dementia and is characterized by reports of memory symptoms, abnormal memory for age, and impairments in other cognitive domains such as executive function, language, orientation.²⁶

Search Methods

A literature search was conducted by 2 investigators (X.S. and Z.Z.) using PubMed, Embase, and Web of Science on September 15, 2020, using the keywords search strategy *vision impairment* combined with *dementia*, *Alzheimer's disease*, *cognitive impairment* or *cognition* (the search strategy is detailed in Table S1, available at www.aaojournal.org). We also reviewed references cited by the included studies and citations of the included publications (Google Scholar) to retrieve other potentially relevant studies. The search was restricted to adults, but without language restriction. We also searched for eligible unpublished large-scale cohort studies and identified 7 cohort studies with relevant data. Access to unpublished data from 4 studies, the China Health and Retirement Longitudinal Study,²⁷ the Health and Retirement Study (HRS),²⁸ the Mexican Health and Ageing Study,²⁹ and the UK Biobank,³⁰ were granted. The data were analyzed and incorporated in the meta-analysis (detailed methods can be seen in Supplemental Text, available at www.aaojournal.org).

Study Selection and Risk of Bias Assessment

Two reviewers (X.S. and Z.Z.) independently screened the titles and abstracts of studies to identify articles relevant to vision impairment and dementia or cognitive impairment. The 2 team members also independently reviewed the full text of the remaining studies to assess the study design. Studies with a study design that did not meet the inclusion criteria were excluded. Finally, we assessed the quality of the remaining studies using the Newcastle-Ottawa Scale.²³ Discrepancies were solved by discussion and consensus.

Data Collection

Two reviewers (X.S. and Z.Z.) independently extracted data into a customized database using a predefined data extraction sheet (Excel; Microsoft Corporation, Redmond, WA). Extracted data included first author name, publication year, cohort name, country where the study was conducted, the year during which baseline data were collected, follow-up duration, number of participants, gender, age at baseline, RRs, and 95% CIs for dementia and cognitive impairment associated with vision impairment, the methods used to assess vision impairment, and methods used to identify events.

Grading of Evidence

The overall certainty of the body evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation approach. By this approach, the evidence can be graded as being of high, moderate, low, or very low quality; however, evidence derived from observational studies receive an initial grade of low.³¹

Criteria for downrating the quality of evidence include risk of bias (low Newcastle-Ottawa Scale score),³² imprecision (the 95% CI for risk estimates are wide or cross a minimally important difference of 10% for benefit or harm),³³ inconsistency (substantial unexplained interstudy heterogeneity, $I^2 > 50\%$),³⁴ indirectness (presence of factors that limit the generalizability of the results),³⁵ and publication bias (evidence of small-study effects). Scores for observational analyses can be upgraded for a large magnitude of effect (RR, ≥ 2 or ≤ 0.5), dose-response gradient, or attenuation by plausible confounding.³⁶

Data Synthesis and Analysis

Pooled estimates across studies were obtained using random-effects meta-analysis, after log-transformation of the study-specific estimates. Study weights were calculated from the inverse of the variance of the log RR.³⁷ For studies that reported RRs of dementia only for subgroups (such as moderate and severe vision impairment),^{18,20,38,39} the pooled RR using random-effects models for the corresponding study was used in the meta-analysis. Risk estimates from the most fully adjusted models were used in the estimation of the pooled RR. Random-effects models taking into account both within-study and between-study variability were used to estimate pooled RRs for associations of vision impairment with incident dementia and cognitive impairment.

Secondary analyses were conducted to examine whether the association of vision impairment with incident dementia and cognitive impairment differed across subgroups of important variables. Stratified analyses were performed for these variables: the length of follow-up, methods used to assess vision, geographical region, and study quality that were available in the included prospective studies.

As a value for describing the proportion of the total variation in study estimates, I^2 was used to test between-study heterogeneity (25%, 50%, and 75% for low, moderate, and high heterogeneity, respectively).⁴⁰ Several commonly used methods—Egger's test and funnel plots, trim and fill, as well as the calculation of pooled estimates of remaining studies by removing 1 study at a time—were applied to investigate publication bias. Publication bias for the primary analysis was assessed first using Egger's test and funnel plots for asymmetry. Trim-and-fill analysis then was used to adjust RRs (95% CIs) for the presence of publication bias. A sensitivity analysis also was conducted to calculate the pooled estimates of remaining studies by removing 1 study at a time to determine whether the association was dependent on a particular study.

Population-attributable risk (PAR) of incident dementia associated with vision impairment was computed for each country using the following formula:

$$\text{PAR\%} = \frac{p \times (\text{RR} - 1)}{p \times (\text{RR} - 1) + 1} \times 100$$

where p represents the proportion of vision impairment and RR represents the pooled RR for incident dementia associated with vision impairment based on our meta-analysis. The prevalence of vision impairment in 2015 for each country estimated by the Global Burden of Disease Study was used in the analysis.⁴¹ The

global burden of dementia associated with vision impairment as well as the burden for each country then was calculated. The number of people with dementia in 2016 for each country was based on the data estimated by the Global Burden of Disease Study in 2016.¹ The meta-analysis was performed with STATA software version 13.1 (StataCorp, College Station, TX).

Results

Characteristics of Studies

A total of 13 917 articles were identified, with 92 remaining after a review of the titles and abstracts. Only 38 prospective cohort studies (36 plus 2 additional studies retrieved through the citations or references) reported the association of vision impairment with incident dementia or cognitive impairment. These 38 articles, with the addition of the unpublished results of the China Health and Retirement Longitudinal Study, HRS, Mexican Health and Ageing Study, and the UK Biobank, were included in the systematic review (Fig 1). Seven cohort studies reporting only the association between vision impairment and cognitive decline and 11 investigating the association between causes of vision impairment (age-related macular degeneration, cataract, glaucoma, and diabetic retinopathy) and dementia or Alzheimer's disease were excluded from the meta-analysis. Two studies were excluded from the meta-analysis because the quality score was 5 or less,^{42,43} and 22 cohort studies were included in the meta-analysis. Ten prospective studies investigated the association between vision impairment and incident dementia only,^{18–21,38,44–46} 8 studies investigated the association between vision impairment and incident cognitive impairment only,^{39,47–52} and 4 studies investigated the association between vision impairment and incidence of both dementia and cognitive impairment.^{17,53,54} The primary end point was dementia rather than Alzheimer's disease in the meta-analysis because all the included studies reported the association between vision impairment and dementia and only several studies reported the results for Alzheimer's disease.

Data for 6 204 827 individuals (50.9% women) from 14 studies were available for the meta-analysis of the association between vision impairment and dementia, among which 171 888 cases of dementia were newly identified. The number of participants in each study ranged from 625 to 6 029 657. Thirteen studies were conducted of both men and women and 1 was conducted of women only. Seven studies were conducted in North America, 3 were conducted in Asia, 3 were conducted in Europe, and 1 was conducted in Australia. The mean duration of follow-up for the analysis of dementia ranged from 3.7 to 14.5 years (Table 1). The vision was assessed using charts in 8 studies and using self-reported scales in 6 studies (Table S2, available at www.aaojournal.org). Nine of 14 studies showed a high overall risk of bias (Newcastle-Ottawa quality score, ≤ 7). The most common limitations in the studies were loss to follow-up, ascertainment of exposure, and short duration of follow-up (Table S3, available at www.aaojournal.org).

For the meta-analysis of the association between vision and cognitive impairment, data for 45 313 individuals (57.8% women) from 12 studies were available, among which 13 350 cases of cognitive impairment were newly identified. The number of participants in each study ranged from 625 to 19 618. Ten studies were conducted of both women and men and 2 studies were conducted of women only. Eight studies were conducted in North America, 2 studies were conducted in Australia, 1 study was conducted in Asia, and 1 study was conducted in Europe. The mean duration for the analysis of cognitive impairment ranged from 3 to 18 years (Table 2). Vision impairment was defined by charts in 6 studies and

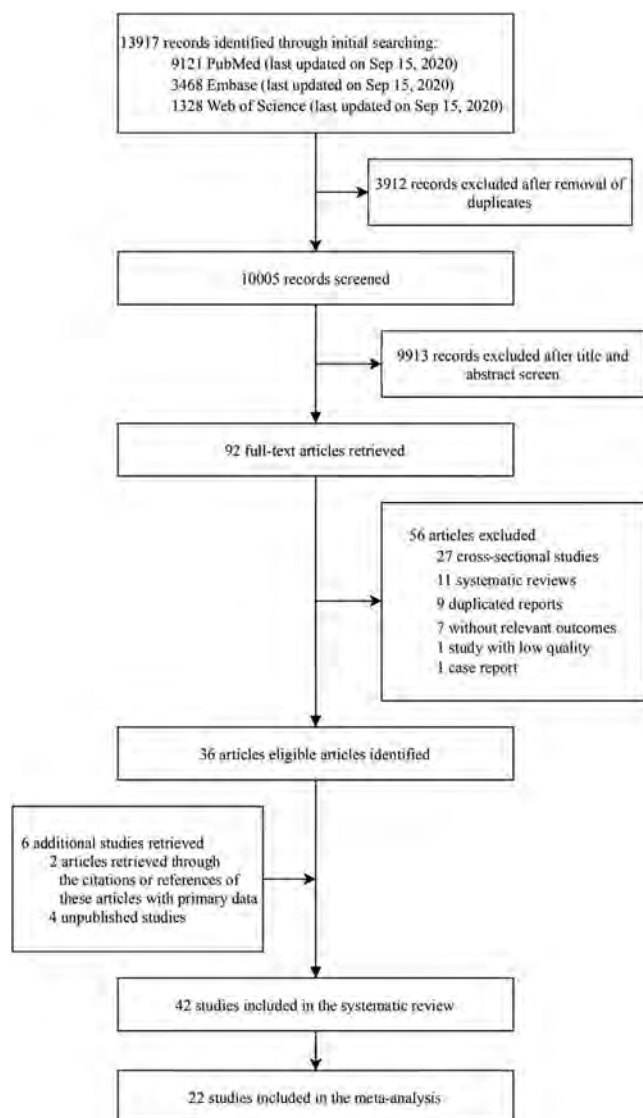


Figure 1. Flowchart showing study selection.

by self-reported scales in 6 studies (Table S4, available at www.aaojournal.org). Nine of 12 studies showed high overall risk of bias with Newcastle-Ottawa quality scores of 7 or less. The most common limitations in the studies were loss to follow-up, ascertainment of exposure, and nonrepresentativeness (Table S5, available at www.aaojournal.org).

Eye Disease and Incident Dementia

As shown in Table S6 (available at www.aaojournal.org), 4 of 7 cohort studies found a positive association between age-related macular degeneration and incident dementia^{15,55,56} (including the unpublished data from the UK Biobank), and the 3 remaining studies did not find a significant association.^{57–59} Three of 8 cohort studies showed a positive association,^{16,60,61} 1 study found an inverse association between glaucoma and incident dementia,⁵⁸ and 4 studies did not find a significant association^{55,62} (including the unpublished data from the UK Biobank and HRS). Two of 4 cohort studies demonstrated that cataract was associated with an increased risk of dementia⁵⁸ (including the unpublished data from the UK Biobank), and the 2 remaining studies did not find

a significant association.^{55,61} Two of 3 cohort studies demonstrated that diabetic retinopathy was associated with an increased risk of dementia⁵⁸ (including the unpublished data from the UK Biobank), and the other study did not find a significant association.⁵⁵

Vision Impairment and Incident Dementia

For the meta-analysis, the pooled RR from the random-effects model for incident dementia associated with vision impairment was 1.47 (95% CI, 1.36–1.60), and moderate heterogeneity was found ($I^2 = 48.0\%$; $P = 0.023$; Fig 2). No significant publication bias was observed based on Egger's test ($P = 0.45$) or the visual inspection of the funnel plot (Fig S1, available at www.aaojournal.org). The adjusted RR of incident dementia associated with vision impairment using trim-and-fill analyses was 1.47 (95% CI, 1.09–1.99). The associations of vision impairment with incident dementia were similar across methods of vision assessment, length of follow-up, and study quality. This association was significant in North America (RR, 1.53; 95% CI, 1.31–1.77) and Europe (RR, 1.57; 95% CI, 1.29–1.92), but not in Asia (RR, 1.44; 95% CI, 0.93–2.23; Fig 3). Sensitivity analysis showed that the pooled estimate of the effect of vision impairment on the risk of dementia did not change with the removal of any 1 study (Table S7, available at www.aaojournal.org).

Vision Impairment and Incident Cognitive Impairment

All 7 cohort studies found that vision impairment was associated with a greater decline in the cognitive score during follow-up (Table S8, available at www.aaojournal.org).^{8–14} For the meta-analysis, a positive association was found between vision impairment and incident cognitive impairment (RR, 1.35; 95% CI, 1.28–1.41) from the random-effects model with no heterogeneity ($I^2 = 15.6\%$; $P = 0.29$; Fig 4). No significant publication bias based on Egger's test ($P = 0.10$) or the visual inspection of the funnel plot (Fig S2, available at www.aaojournal.org) was found. The adjusted RR of incident cognitive impairment associated with vision impairment using trim and fill analyses was 1.34 (95% CI, 1.02–1.75). The associations of vision impairment with incident cognitive impairment were significant across methods of vision assessment, length of follow-up, study quality, and geographical region (Fig 5). Sensitivity analysis showed that the pooled estimate of the effect of vision impairment on the risk of cognitive impairment did not change with the removal of any 1 study (Table S9, available at www.aaojournal.org).

Grading of Recommendations Assessment, Development and Evaluation Assessment

Although no downgraded factors were identified, the overall certainty of the body evidence was graded as low for as the default level for observational studies (Table S10, available at www.aaojournal.org).

Global Burden of Dementia by Vision Impairment

The global number of people with dementia in 2016 associated with moderate or severe vision impairment was 2.1 (80% uncertainty interval [UI], 1.0–3.3 million), which accounted for 4.7% (80% UI, 2.3%–7.5%) of the global burden of dementia. An inverse association was found between income and the burden of dementia associated with vision impairment with the PAR as 2.2%

Table 1. Study Design Characteristics of Prospective Cohort Studies of Vision Impairment and Dementia

Study	Baseline Study Years	Country Cohort	No. of Participants/ Cases	Population	Age (yrs)	Gender (% Female)	Duration (yrs)	Adjustment for Potential Confounders*	Newcastle Score [†]
Rogers et al, 2010	1992–1993	United States	625/168	Aging, Demographics, and Memory Study	≥ 50	61.4	10.9 (3.5–13.0)	Age, method version (before or after September 1994), season, total energy, education, smoking, alcohol intake, leisure-time physical activity, and BMI	7
Lipnicki et al, 2017	2005	Australia	873/71	The Sydney Memory and Ageing Study	70–90	56.1	6.0	Age, gender, and education	6
Davies-Kershaw et al, 2018	2002–2003	UK	8648/275	English Longitudinal Study of Ageing	≥ 50	52.5	11	Age, gender, wealth, education, cardiovascular risk factors	8
Brenowitz et al, 2019	1999–2002	United States	1818/336	Health, Aging, and Body Composition Study	70–79	51.8	10	Age, race, gender, education, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, smoking status, alcohol use, and physical activity	8
Naël et al, 2019	1999–2001	France	7736/882	Three-City Study	≥ 65	61.3	12	Center, age, gender, educational level, hearing loss, living alone, income, depressive symptomatology at baseline, smoking habits, BMI, hypertension, history of stroke, history of cardiovascular disease, hypercholesterolemia, hypertriglyceridemia, diabetes, and APOE4 genotype	9
Postuma et al, 2019		United States	1280/352		66.3 (8.4)	17.5	4.6 (1–19)	Age, gender, and center	7
Tran et al, 2020	2000–2002	United States	1061/52	Women's Health Initiative Memory Study	73.8 (3.7)	100	3.8	Age, race or ethnicity, hormone therapy, self-reported educational level, self-reported physical activity, self-reported hearing loss, smoking status, cognitive score at baseline, and self-reported systemic comorbidities (depression, cardiovascular disease, congestive heart failure, hypertension, hyperlipidemia, chronic pulmonary disease, peptic ulcer disease, liver disease, leukemia or lymphoma, and diabetes)	7

(Continued)

Table 1. (Continued.)

Study	Baseline Study Years	Country Cohort	No. of Participants/ Cases	Population	Age (yrs)	Gender (% Female)	Duration (yrs)	Adjustment for Potential Confounders*	Newcastle Score [†]
Lee et al, 2020	2005	China (Hong Kong)	15 576/1349	The cohort of the Elderly Health Centres	74.5 (4.8)	64	5 (3–6)	Age, gender, educational level, socioeconomic status, cataract, glaucoma, cardiovascular risks, hearing impairment, poor mobility, depression, physical exercise, intellectual activities, social activities, fruit and vegetable consumption, and smoking	9
Maruta et al, 2020	2010	Japan	2190/1153	Japanese government implemented the long-term care insurance system	78.9 (6.1)	79.4	8	Age, gender, care-need level, and degree of independent daily living for disabled older adults	7
Paik et al, 2020	2009–2010	Korean	6 029 657/165 293		≥40	50.7	5.7 (0.9)	Age, gender, smoking, drinking levels, regular exercise, diabetes, hypertension, and lipid levels	6
Hwang et al, 2020	2000–2002	United States	2051/321	The Ginkgo Evaluation of Memory Study	≥ 75	44.1	5.6	Age, gender, race, education, income, BMI, alcohol intake, smoking status, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, clinic site, treatment status, and APOE	7
Zhu et al, 2020	2009	United Kingdom	117 187/438	UK Biobank	40–69	54.4	6.0	Age, gender, race or ethnicity, education level, Townsend index, physical activity level, family history of dementia, history of diabetes mellitus, hypertension, and depression	8
Shang et al, 2020 [‡]	2012	United States	9012/148	The Health and Retirement Study	≥ 50	48.7	3.7 (1.0–5.7)	Age, gender, education, alcohol intake, smoking, physical activity, BMI, hypertension, diabetes, heart disease, stroke, lung disease, psychiatric disorders, and arthritis	7
Shang et al, 2020	2001–2003	Mexico	7113/1050	Mexican Health and Aging Study	≥ 50	58.8	14.5 (2.3)	Age, gender, education, living area (rural and urban), follow-up duration, alcohol intake, smoking, BMI, hypertension, diabetes, and depression	7

BMI = body mass index.

*Prospective studies reporting relative risks adjusted for at least age and gender were included in the meta-analysis.

[†]Study quality was assessed using the Newcastle-Ottawa scale. Scores for each item are shown in [Table S3](#).

[‡]Unpublished data from the Health and Retirement Study were analyzed and incorporated in the meta-analysis. The Health and Retirement Study is grateful to the Division of Behavioral and Social Research of the National Institute on Aging of the National Institutes of Health for primary support of this project (U01 AG009740) and to the Social Security Administration for substantial cofunding. The Mexican Health and Aging Study is supported by the National Institutes of Health/National Institute on Aging (grant no.: R01AG018016 [R. Wong, PI]) and by the INEGI in Mexico. The use of UK Biobank data is supported by the Fundamental Research Funds of the State Key Laboratory of Ophthalmology; the Project of Investigation on Health Status of Employees in Financial Industry in Guangzhou, China (grant no.: Z012014075); and the Science and Technology Program of Guangzhou, China (grant no.: 202002020049). No conflict of interest disclosures were declared for any of these studies.

Table 2. Characteristics of Prospective Cohort Studies of Vision Impairment and Cognitive Impairment

Study	Baseline Study Dates	Country	No. of Participants/ Cases	Population	Age (yrs)	Gender (% Female)	Duration (yrs)	Adjustment for Potential Confounders*	Newcastle Score [†]
Tran et al, 2020	2000–2002	United States	1061/48	Women's Health Initiative Memory Study	73.8 (3.7)	100	3.8	Age, race or ethnicity, hormone therapy (based on the trial arm), self-reported educational level, self-reported physical activity, self-reported hearing loss, smoking status, cognitive score at baseline, and self-reported systemic comorbidities (depression, cardiovascular disease, congestive heart failure, hypertension, hyperlipidemia, chronic pulmonary disease, peptic ulcer disease, liver disease, leukemia or lymphoma, and diabetes)	7
Rogers et al, 2010	1992–1993	United States	625/169	Aging, Demographics, and Memory Study	≥ 50	61.4	10.9 (3.5–13.0)	Age, method version (before or after September 1994), season, total energy, education, smoking, alcohol intake, leisure-time physical activity, and BMI	7
Fischer et al, 2016	1993–1995	United States	1884/192	The Epidemiology of Hearing Loss Study	66.7 (8.4)	59.1	10	Age, gender, education, smoking status, BMI, exercise, alcohol consumption, hypertension, diabetes mellitus, no. of high inflammatory markers, non-HDL cholesterol, mean intima-media thickness, frailty score, longest-held job, cold or stuffy nose, nasal polyps, deviated septum, allergies, head injury, stroke or transient ischemic attack, and epilepsy	9
Dearborn et al, 2018	2001–2006	United States	655/33	Maine-Syracuse Longitudinal Study		60.0	5	Age, gender, education, ethnicity, Center for Epidemiologic Studies Depression Scale score, physical function, chronic kidney disease, and total homocysteine	6
Ward et al, 2018	1986–1988, 1997–1998	United States	1352/536	Study of Osteoporotic Fractures	77.7 (3.3)	100	10	Age, race, education, alcohol use, history of diabetes, history of hypertension, Geriatrics Depression score, and baseline cognitive score	7
Swenor et al, 2019	1999–2002	United States	2034/1303	Health, Aging, and Body Composition Study	70–79	52.2	9	Year, age, gender, race, depression, diabetes, education, smoking, and study site	8
Hong et al, 2016	1992–1994	Australia	860/174	Blue Mountains Eye Study	≥ 50	42.9	10	Age and gender	7
Luck et al, 2010	2003	German	2331/350	Longitudinal German Study on Ageing, Cognition and Dementia in Primary Care Patients	≥ 75	65.1	3	Age, gender, living situation, comorbidity other than hyperlipidemia, transient ischemic attack, impairment in vision, smoking, alcohol consumption, familial history of dementia, and the use of antidementia drugs	6

(Continued)

Table 2. (Continued.)

Study	Baseline Study Dates	Country	No. of Participants/ Cases	Population	Age (yrs)	Gender (% Female)	Duration (yrs)	Adjustment for Potential Confounders*	Newcastle Score [†]
Maharani et al, 2020	1996–2010	United States	19 618/7536	Health and Retirement Study	57.8 (6.2)	55.4	18	Age, gender, marital status, education and wealth; full adjustment: adjusted for age, gender, marital status, education, wealth, smoking and drinking behavior, physical exercise, depression scores, and no. of comorbidities	8
Lipnicki et al, 2017	2005	Australia	873/210	Sydney Memory and Ageing Study	70–90	56.1	6.0	Age, gender, and education	6
Shang et al, 2020	2011	China	8227/1494	The China Health and Retirement Longitudinal Study [‡]	60.1 (7.1)	50.5	4	Age, gender, education, smoking, alcohol intake, physical activity, cognitive score at baseline, BMI, hypertension, diabetes, heart disease, stroke, lung disease, psychiatric disorders, arthritis, and cancer at baseline	7
Shang et al, 2020	2001–2003	Mexico	5793/1305	Mexican Health and Aging Study	≥ 50	58.9	14.2 (2.4)	Age, gender, education, living area (rural and urban), follow-up duration, alcohol intake, smoking, BMI, hypertension, diabetes, and depression	7

BMI = body mass index.

*Prospective studies reporting relative risks adjusted for at least age and gender were included in the meta-analysis.

[†]Study quality was assessed using the Newcastle-Ottawa scale. Score for each item is shown in Table S5.

[‡]The China Health and Retirement Longitudinal Study is supported by the Behavioral and Social Research division of the National Institute on Aging of the National Institutes of Health (grant nos.: 1-R21-AG031372-01, 1-R01-AG037031-01, and 3-R01AG037031-03S1); the National Science Foundation of China (grant nos.: 70773002, 70910107022, and 71130002), the World Bank (contract nos.: 7145915 and 7159234), and Peking University. The Mexican Health and Aging Study is supported by the National Institutes of Health/National Institute on Aging (grant no.: R01AG018016 [R. Wong, PI]) and by the INEGI in Mexico. No conflict of interest disclosures were declared for either of these 2 studies.

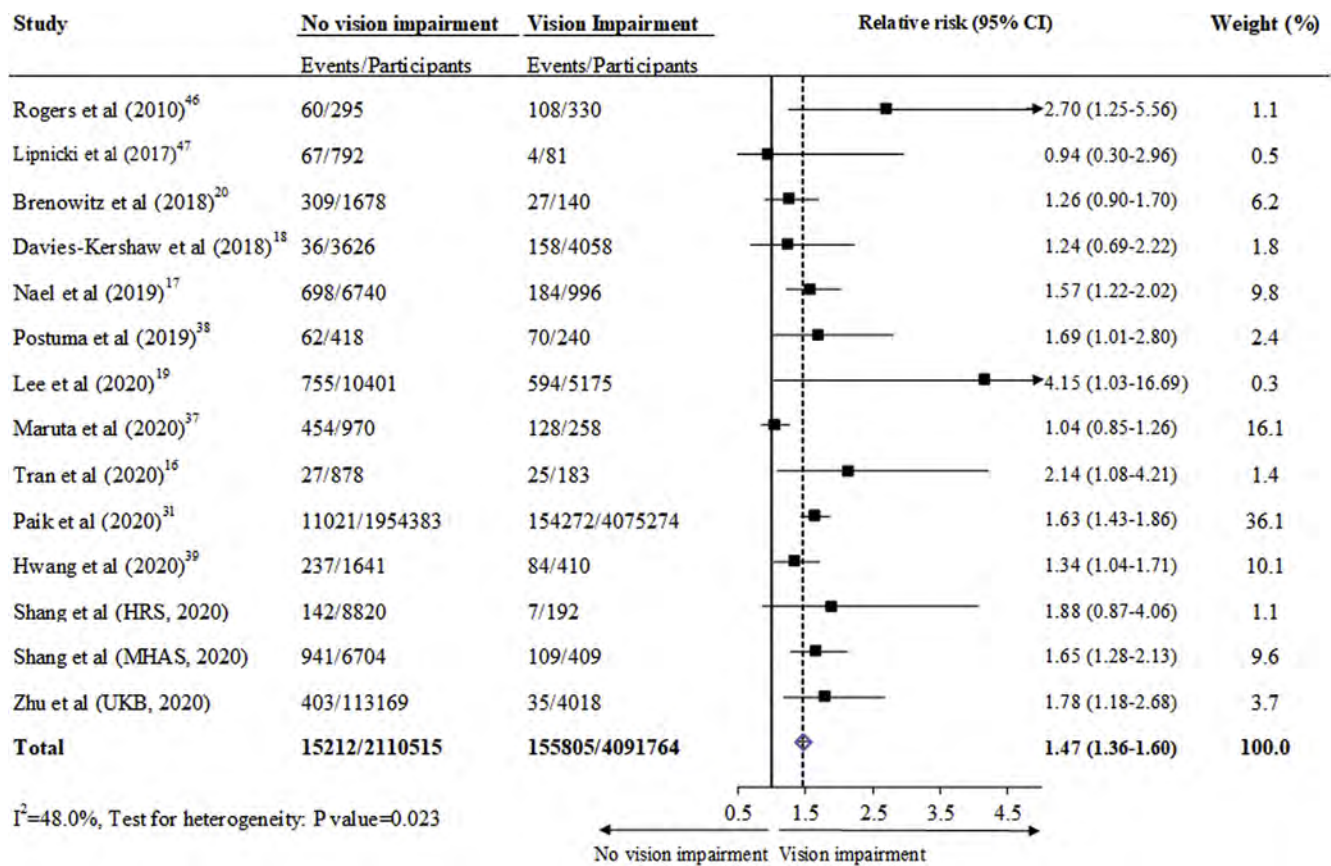


Figure 2. Forest plot showing the relative risk of incident dementia in participants with and without vision impairment in prospective cohort studies. Central squares of each horizontal line represent the relative risk for each study. Horizontal lines indicate the range of the 95% confidence interval (CI), the vertical solid line indicates the relative risk of 1.0, and the vertical dash line indicates the pooled relative risk of included prospective cohort studies.

(80% UI, 1.0%–3.6%), 5.7% (80% UI, 2.9%–9.0%), and 6.6% (80% UI, 3.2%–10.2%) in high-income, middle-income, and low-income countries, respectively. Africa had the largest PAR for dementia resulting from vision impairment (PAR, 6.3%; 80% UI, 3.1%–9.8%), followed by Asia (PAR, 5.8%; 80% UI, 2.9%–8.9%) and Latin America and the Caribbean (PAR, 3.5%; 80% UI, 1.5%–5.9%). North America (PAR, 2.2%; 80% UI, 0.9%–3.6%) and Europe (PAR, 2.2%; 80% UI, 1.0%–3.8%) had the lowest PAR (Table 3).

The largest number of people with dementia associated with vision impairment resided in China (547.0 thousand; 80% UI, 257.2–880.4 thousand), India (218.5 thousand; 80% UI, 117.7–327.0 thousand), the United States (88.5 thousand; 80% UI, 38.2–145.8 thousand), Turkey (73.8 thousand; 80% UI, 41.9–105.7 thousand), and Indonesia (72.1 thousand; 80% UI, 36.7–109.6 thousand; Table S11, available at www.aojournal.org).

Discussion

The present meta-analysis of prospective cohort studies with low-certainty evidence (Grading of Recommendations Assessment, Development and Evaluation approach) demonstrated a positive association of vision impairment with the incidence of both dementia and cognitive

impairment. Individuals with vision impairment showed a 47% greater risk of dementia developing and a 35% greater risk of cognitive impairment developing compared with those without vision impairment. Vision impairment was a significant contributor to the global burden of dementia in older adults 50 years or older, with a larger PAR in low-income countries.

Several mechanisms are proposed for the positive association between vision impairment and both dementia and cognitive impairment. Older individuals affected by vision impairment are less likely to participate in physical and social activities and have a higher risk of depression predisposing them to cognitive decline.^{63–65} The association between vision impairment and dementia or cognitive impairment in part may be the result of the positive association between vision and hearing impairment and the positive association between hearing impairment and dementia.^{6,66} Of 6 cohort studies examining the association of both vision and hearing impairment with dementia, 5 studies found that vision impairment was a stronger predictor of dementia or cognitive impairment than hearing impairment,^{8,9,14,67,68} and 1 study showed that only hearing, but not vision impairment, was associated an increased risk of dementia.²¹ This suggests that vision impairment is a stronger predictor

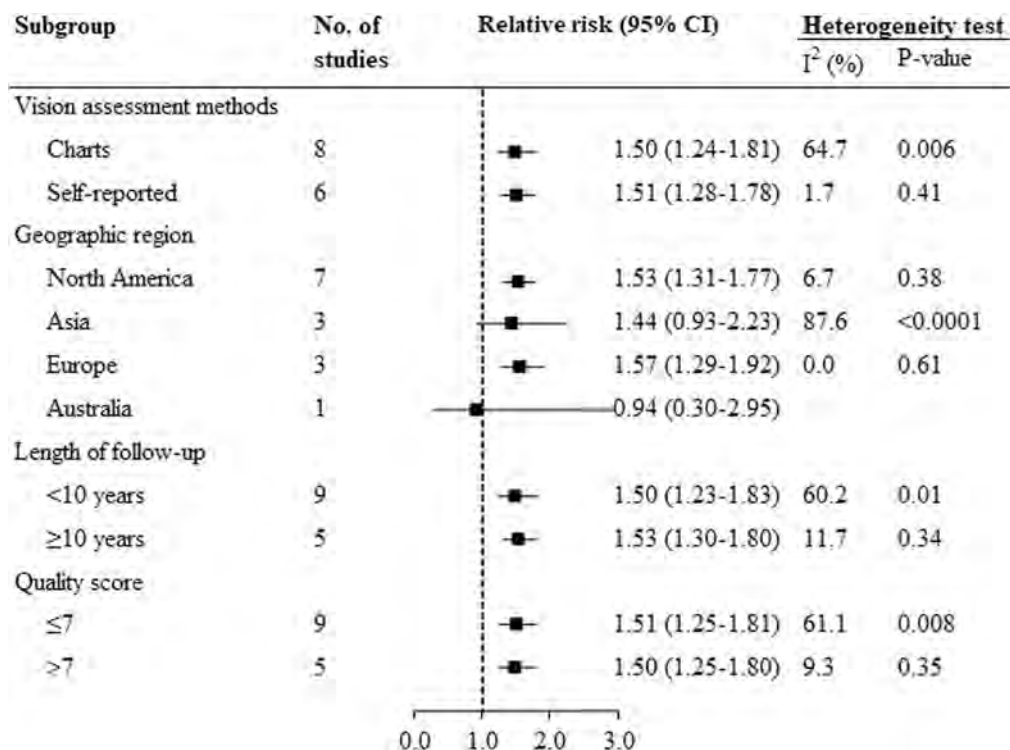


Figure 3. Forest plot showing the stratified analysis of the association between vision impairment and incident dementia. Relative risks (95% confidence intervals [CIs]) and I^2 values were obtained from the meta-analysis with random effects. Study quality was assessed using the Newcastle-Ottawa scale.

of dementia or cognitive impairment even independent of the effect of hearing impairment.^{8,9,67} Loss of visual input may lead to reduced activation of the central sensory pathways, resulting in an increased risk of cognitive load and damage to intrinsic brain structures,^{69,70} which in turn accelerates the rate of cognitive decline. Moreover, recent evidence suggests that vision impairment is one of the first manifestations of the development of dementia.^{71,72} Of note, cognitive decline and vision impairment share many risk factors, including smoking, poor diet quality, hypertension, diabetes, and obesity,^{6,73–75} which also may partly explain the positive association. However, the exact mechanism that underlies the association of dementia with vision impairment requires further exploration in future studies.

Only 40% of the risk of dementia has been attributable directly to modifiable factors globally⁶; therefore, it is imperative to identify additional modifiable risk factors such as vision impairment because more than four-fifths of cases are preventable and treatable. Vision impairment as a risk factor for dementia has prompted increasing attention in the last several years. Ten of 11 prospective cohort studies investigating the association between vision impairment and incident dementia have been published since 2018, with only 1 study published before 2018 (published in 2010). This highlights the mounting interest in targeting vision impairment as an emerging modifiable risk factor for the prevention of dementia.

Several factors may confound the association between vision impairment and dementia. Objective assessment of

vision may be more likely to reflect physiologic decline and may be easier to compare among studies, but self-reported vision may be a better marker of functional performance in activities of daily living and may be aggravated by psychological distress such as depression and social isolation.^{76,77} Our stratified analysis showed that the magnitude of the association between vision impairment and incident dementia was similar among 7 prospective studies with objective vision assessment and 4 prospective studies with subjective vision assessment. This suggests that the association between vision impairment and dementia is independent of the type of vision assessment methods used in the studies. Data from the Three-City Study of 7736 initially dementia-free participants 65 years of age or older with 12 years of follow-up showed that near vision impairment was associated with an increased risk of dementia in the first 2 years (HR, 1.95; 95% CI, 1.16–3.28) and from 2 to 4 years (HR, 1.82; 95% CI, 1.07–3.08), but not beyond 4 years' duration (HR, 1.34; 95% CI, 0.95–1.89).¹⁸ The findings of this study suggest that there may be a decreasing trend in the magnitude between the association between vision impairment and dementia with increasing follow-up. However, our stratified analysis showed that the pooled RR for studies with follow-up of 10 years or more (1.48; 95% CI, 1.18–1.86) was similar for those with follow-up of less than 10 years (1.49; 95% CI, 1.19–1.88). The risk factors of dementia such as obesity, hypertension, and diabetes also may confound the associations; however, these factors were adjusted for in most of the studies included in the meta-analysis, suggesting that the

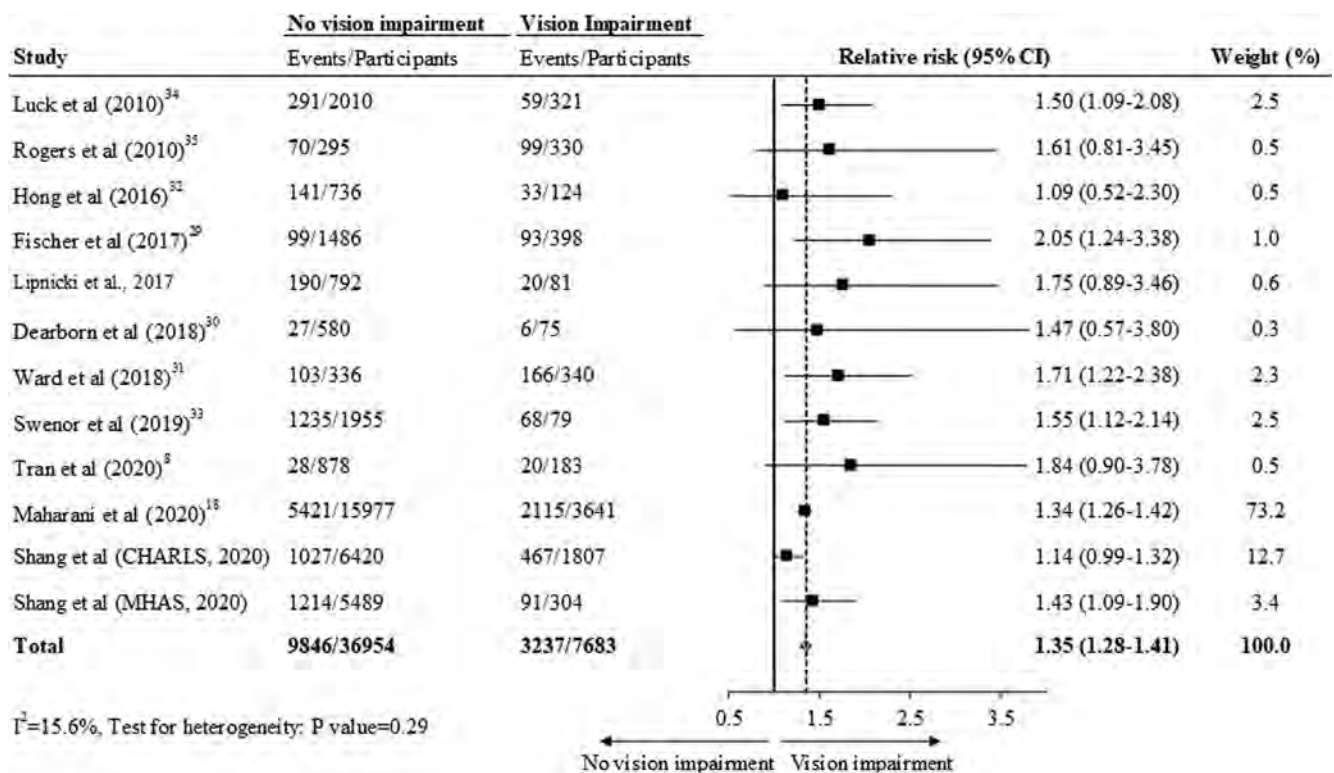


Figure 4. Forest plot showing the relative risk of incident cognitive impairment in participants with and without vision impairment in prospective cohort studies. Central squares of each horizontal line represent the relative risk for each study. Horizontal lines indicate the range of the 95% confidence interval (CI), the vertical solid line indicates the relative risk of 1.0, and the vertical dash line indicates the pooled relative risk of included prospective cohort studies.

association between vision impairment and dementia also was independent of these confounders. However, 13 of the 14 studies included in the meta-analysis were conducted in 7 high-income countries; therefore, this association needs to be explored in other countries with greater socioeconomic diversity, especially low- and middle-income countries.

The attributable risk of dementia associated with vision impairment (4.5%) was comparable even with that of well-known risk factors for dementia including depression (10.6%), physical inactivity (9.6%), social isolation (4.2%), and diabetes (3.1%), as shown in the 2020 report of the Lancet Commission.⁶ Economic inequality was evident in PAR of dementia associated with vision impairment. The largest number of people with dementia associated with vision impairment resided in low- and middle-income countries, including China, India, Indonesia, and Pakistan, which was attributed mainly to the high prevalence of vision impairment and a large number of older adults in these countries. An inverse association was reported between economic indicators and both rates of cataract surgery and glaucoma treatment.^{78,79} A high proportion of people with vision impairment associated with eye diseases such as cataract and glaucoma were not diagnosed or treated especially in low- and middle-income countries.^{78–80} Notably, the proportion of blindness or vision impairment that can be preventable or treatable among the global population decreased from 81.7% in 2010 to 81.2% in 2015 and

is projected to decrease further to 80.0% in 2020.^{7,81} Although the age-standardized prevalence of avoidable vision impairment showed no change (0.5%) between 2010 and 2019, the number of cases increased by 31.5% because of the increasing global ageing population.⁷ Vision impairment as a modifiable risk factor warrants careful scrutiny given that rehabilitation of vision impairment such as cataract surgery and visual training may help to prevent or delay cognitive decline in older adults.^{82,83} Therefore, screening and treating for vision impairment in older adults, especially in low- and middle-income countries, may mitigate the global burden of dementia significantly.

To the best of our knowledge, no previous meta-analysis of longitudinal studies has examined comprehensively the association of vision impairment with incident dementia and cognitive impairment. We also uniquely estimated the global burden of dementia associated with vision impairment. The meta-analysis had some limitations. First, it is possible that the measures for cognition using visual stimuli may overestimate the association between vision impairment and dementia or cognitive impairment, although the use of the modified Mini-Mental State Examination or the Telephone Interview for Cognitive Status for cognitive assessment in most of the included studies may not be overly difficult even for participants with vision impairment.^{84,85} Second, data for the association between vision

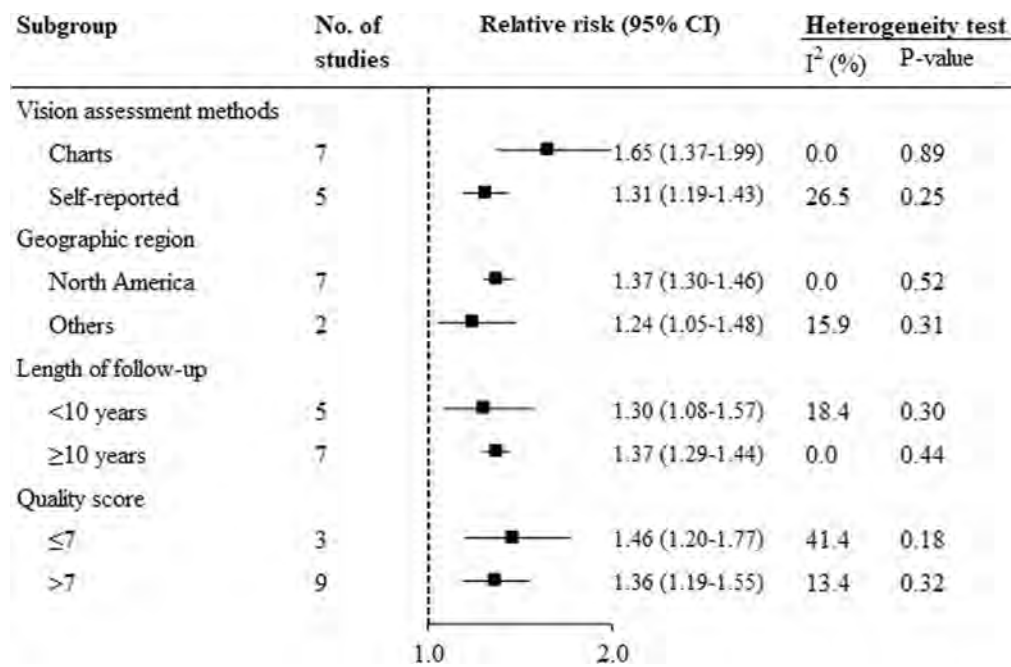


Figure 5. Forest plot showing the stratified analysis of the association between vision impairment and incident cognitive impairment. Relative risks (95% confidence intervals [CIs]) and I^2 values were obtained from the meta-analysis with random effects. Study quality was assessed using the Newcastle-Ottawa scale.

impairment and specific types of dementia, such as Alzheimer's disease and vascular dementia, were reported in only 2 studies, which severely limits the ability to conduct a subgroup analysis. Nonetheless, both studies found that vision impairment was associated with an increased risk of Alzheimer's disease, which is consistent with our findings for the association between vision impairment and incident dementia. Third, a meta-analysis of the association between the main causes of vision impairment and incident dementia was not conducted because only several previous prospective studies reported the association of cataract, glaucoma, diabetic retinopathy, or age-related macular degeneration with the incidence of

dementia. Fourth, a relatively small number of cohort studies were included in the meta-analysis. In particular, 2 of 14 prospective cohort studies examining the association between vision impairment and incident dementia had a full Newcastle-Ottawa quality score of 9^{18,20}; therefore, more high-quality research is needed to examine this association. Fifth, RRs for cognitive impairment associated with vision impairment in studies with different follow-up periods may not be comparable (duration of follow-up was not controlled in 5 of 12 included studies), although we have pooled RRs for studies with a length of follow-up of less than 10 years and of 10 years or more. Sixth, although the time points and duration of the follow-up are totally

Table 3. Global Burden of Dementia Associated with Vision Impairment

Region	Population-Attributable Risk (80% Uncertainty Interval)*	Counts (80% Uncertainty Interval)†
World	4.7% (2.3%–7.5%)	2 055 938 (992 714–3 266 282)
World Bank income groups		
High-income countries	2.2% (1.0%–3.6%)	367 467 (170 420–602 426)
Middle-income countries	5.7% (2.9%–9.0%)	1 476 532 (733 262–2 302 929)
Low-income countries	6.6% (3.2%–10.2%)	74 909 (37 029–116 114)
Geographic regions		
Africa	6.3% (3.1%–9.8%)	143 418 (70 834–221 662)
Asia	5.8% (2.9%–8.9%)	1 384 106 (703 123–2 137 992)
Europe	2.2% (1.0%–3.8%)	202 520 (86 941–344 236)
Latin America and the Caribbean	3.5% (1.5%–5.9%)	133 084 (56 949–222 009)
North America	2.2% (0.9%–3.6%)	94 433 (41 091–156 132)
Oceania	2.7% (1.2%–4.5%)	7452 (3363–12 416)

*Computed based on the prevalence of vision impairment in 2015 for each country estimated by the Global Burden of Disease Study and the pooled relative risk for incident dementia associated with vision impairment in our meta-analysis.

†Computed based on the number of people living with dementia for each country estimated by the Global Burden of Disease Study.

different between the study by Rogers and Langa⁵³ (1992–2005) and the HRS (2012–2016) included in the meta-analysis, some potential overlap may exist between the 2 studies. However, our sensitivity analysis showed that the pooled RRs of the remaining studies by removing the study by Rogers et al (pooled RR, 1.46; 95% CI, 1.35–1.59) or the HRS (pooled RR, 1.49; 95% CI, 1.30–1.71) did not differ significantly (Table S7). Seventh, prospective cohort studies from only 7 countries reporting the association between vision impairment and dementia were included in the meta-analysis; therefore, the pooled RR used to estimate the PAR for some countries may be biased. Finally,

the number of cases of dementia associated with vision impairment may have been overestimated in our study because the calculation of PAR is not weighted for communality of risk factors (the proportion of variance in vision impairment accounted for by all risk factors).

In conclusion, vision impairment is associated with an increased risk of both dementia and cognitive impairment in older adults. Vision impairment is an important modifiable contributor to dementia, and screening and treating vision impairment, especially in low- and middle-income countries, may help to alleviate the global burden of dementia.

Footnotes and Disclosures

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¹ Guangdong Eye Institute, Department of Ophthalmology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China.

² State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China.

³ Centre for Eye Research Australia, Melbourne, Australia.

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Author Contributions:

Conception and design: Shang, Wang, He

Analysis and interpretation: Shang, Zhu, Wang

Data collection: Shang, Zhu

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Abbreviations and Acronyms:

CI = confidence interval; **HR** = hazard ratio; **HRS** = Health and Retirement Study; **PAR** = population-attributable risk; **RR** = relative risk; **UI** = uncertainty interval.

Keywords:

Cognitive impairment, Dementia, Meta-analysis, Population-attributable risk, Vision impairment.

Correspondence:

Mingguang He, MD, PhD, Centre for Eye Research Australia, 75 Commercial Road, Level 6, Melbourne, Victoria 3004, Australia. E-mail: mingguang_he@yahoo.com.

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