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The Bidirectional Relationship between Vision and Cognition

A Systematic Review and Meta-analysis

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Topic: Visual impairment (VI) and cognitive impairment (CIM) are prevalent age-related conditions that impose substantial burden on the society. Findings on the hypothesized bidirectional association of VI and CIM remains equivocal. Hence, we conducted a systematic review and meta-analysis to examine this bidirectional relationship.

Clinical Relevance: Sixty percent risk of CIM has not been well elucidated in the literature. A bidirectional relationship between VI and CIM may support the development of strategies for early detection and management of risk factors for both conditions in older people.

Methods: PubMed, Embase, and Cochrane Central registers were searched systematically for observational studies, published from inception until April 6, 2020, in adults 40 years of age or older reporting objectively measured VI and CIM assessment using clinically validated cognitive screening tests or diagnostic evaluation. Meta-analyses on cross-sectional and longitudinal associations between VI and CIM outcomes (any CIM assessed using screening tests and clinically diagnosed dementia) were examined. Random effect models were used to generate pooled odds ratios (ORs) and 95% confidence intervals (CIs). We also examined study quality, publication bias, and heterogeneity.

Results: Forty studies were included (n = 47 913 570). Meta-analyses confirmed that persons with VI were more likely to have CIM, with significantly higher odds of: (1) any CIM (cross-sectional: OR, 2.38 [95% CI, 1.84−3.07]; longitudinal: OR, 1.66 [95% CI, 1.46−1.89]) and (2) clinically diagnosed dementia (cross-sectional: OR, 2.43 [95% CI, 1.48−4.01]; longitudinal: OR, 2.09 [95% CI, 1.37−3.21]) compared with persons without VI. Significant heterogeneity was explained partially by differences in age, sex, and follow-up duration. Also, some evidence suggested that individuals with CIM, relative to cognitively intact persons, were more likely to have VI, with most articles (8/9 [89%]) reporting significantly positive associations; however, meta-analyses on this association could not be conducted because of insufficient data.

Discussion: Overall, our work suggests that VI is a risk factor of CIM, although further work is needed to confirm the association of CIM as a risk factor for VI. Strategies for early detection and management of both conditions in older people may minimize individual clinical and public health consequences. *Ophthalmology 2021;128:981-992 © 2020 by the American Academy of Ophthalmology*

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With 2 billion people estimated to be 60 years of age or older worldwide by 2050,[1] the number of individuals with cognitive impairment (CIM) also is expected to triple by 2050.[2] Presently, cognitive decline is the fifth leading cause of disability for the elderly[3] and imposes a significant physical, psychological, economic, and social burden on patients, caregivers, families, and society.[4,5] Treatment strategies for CIM or dementia are limited.[6] Therefore, identifying potentially modifiable risk factors for CIM and instituting community risk-reduction strategies may be better strategies than pharmaceutical approaches at reducing the burden of disease.[7–9]

Visual impairment (VI) also is an age-related condition and is estimated to affect more than 1 billion individuals by

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2050.[10] It is the third leading cause of disability for the elderly[11] and also has substantial physical, psychological, and social implications on patients and society overall.[5,11] Interestingly, VI has been suggested as one of the early symptoms of dementia.[12] Many studies have reported similar microvascular and neuronal changes in the eye and brain in patients with CIM or dementia.[13–15] In addition, VI and CIM share many risk factors beyond age,[10,16] including vascular and medical comorbidities,[17] physical inactivity,[18,19] and consequences such as functional decline,[11,20] quality-of-life decline,[21,22] and mortality.[2,23] As such, numerous cross-sectional[24–48] and longitudinal[49–62] studies have attempted to document this relationship. However, findings have been equivocal, possibly because of heterogeneity in research methodologies. Moreover, although a bidirectional relationship between VI and CIM (i.e., persons with VI are more likely to develop CIM and those with CIM are at risk of VI) has been hypothesized, very few studies have investigated this specifically.[57] If a bidirectional relationship exists, it may provide opportunities for developing public health strategies for early detection and management of risk factors for both VI and CIM in older people. To address these gaps, we conducted a systematic review and meta-analysis to examine critically the bidirectional associations between VI and CIM. We hypothesized that VI increases the risk of CIM, and vice versa.

Methods

Search Methods for Identifying Studies

We performed a systematic literature search of 3 databases (PubMed, Cochrane Library, and Embase) from inception until April 6, 2020. The core keywords included *visual impairment* AND *cognitive impairment* AND *adult*. Subsequently, filters such as *publication type* and *human* were added to narrow relevant search results. The bibliographies of included articles were hand searched to identify other relevant records. Our full search strategy and Preferred Reporting Items for Systematic Review and Meta-Analyses checklist are reported in Appendices 1 and 2 (available at www.aaojournal.org).

Eligibility Criteria

We structured our eligibility criteria based on the Population, Intervention, Comparison, Outcomes and Study design framework in the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. Because the pathophysiologic processes of Alzheimer's disease may begin 10 to 20 years before the onset of Alzheimer dementia and this may present as mild CIM (MCI),[63–65] middle-aged (40–64 years) and older (≥65 years) adults were included. This increases the relevance of our findings to clinicians and policymakers considering early identification, prevention, and intervention of CIM.

In this study, VI was defined according to visual acuity (VA) or visual field (VF) losses, assessed by objective measurements (e.g., Snellen chart, Early Treatment Diabetic Retinopathy Study chart, Humphrey perimeter), in agreement with the International Classification of Diseases, Eleventh Revision, criteria of VI and blindness. Cognitive impairment was defined as any CIM assessed using clinically validated cognitive screening tests (e.g., the Mini-Mental Status Examination (MMSE) and Montreal Cognitive Assessment) and diagnostic evaluation based on predefined diagnostic criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders IV[66] or National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association[67]). Therefore, the inclusion criteria consisted of (1) adults 40 years of age or older, (2) observational studies (cross-sectional and longitudinal), (3) VI or CIM defined above as the exposures or outcomes, and (4) participants without VI and CIM as the comparators.

The following studies were excluded: (1) reviews; (2) qualitative studies; (3) case reports, case series, and conference abstracts; (4) animal and in vitro or in vivo studies; (5) interventional studies; (6) non-English studies; (7) studies with no clear definitions of the exposure or outcome variables as per our inclusion criteria; (8) studies of special risk groups (e.g., people with diabetes, cancer, or Down's syndrome); and (9) studies with any form of data insufficiency that did not enable us to draw conclusions from or evaluate the study (e.g., lack of statistical analysis).

Study Selection, Data Collection, and Risk of Bias Assessment

Two authors (T.A.V. and B.K.J.T.) assessed the titles and abstracts of the 2174 identified articles independently according to the predefined inclusion and exclusion criteria. If information was insufficient within the abstract, the full-text articles of relevant studies were extracted for further evaluation. If consensus could not be reached, 3 other coauthors (E.K.F., R.E.K.M. and P.G.) were consulted for arbitration.

Data extraction was performed by the first author (T.A.V.) and checked for accuracy by coauthors (B.K.J.T. and A.T.L.G.). Data were extracted from each article based on the Strengthening the Reporting of Observational Studies in Epidemiology statement.[68] We contacted 19 corresponding authors to request unpublished information such as mean age and adjusted odds ratios (ORs),[27–29,31,34,37,39,44,46,47,51,55,57–62,69] of whom 16 replied.

Two authors (T.A.V. and B.K.J.T.) independently assessed the risk of bias of observational studies using the Newcastle-Ottawa scale (NOS).[70] Following past reviews, studies were graded as having high (≥8 stars), moderate (5–7 stars), or low (0–4 stars) quality on the scale of 0 to 10 for cross-sectional studies and 0 to 9 for prospective and case-control studies.[71]

Data Synthesis and Analysis

Statistical analysis was performed by one of the authors (A.T.L.G.) and was reviewed by another author (T.A.V.). We conducted separate meta-analyses of the association between VI and CIM, stratified by study design (cross-sectional or longitudinal) and CIM definition (any CIM measured by screening tests and clinically diagnosed dementia). Clinical evaluation is more specific than screening tests alone in diagnosing CIM. Because too few articles reported on the cross-sectional or longitudinal relationship between VI and MCI, they were excluded from meta-analyses. We chose to meta-analyze ORs because they were the most commonly reported statistical estimates of effect across studies. We assessed and considered between-study heterogeneity as significant if the P value for the Q test was less than 0.10 or if the I^2 statistic was 50% or more.[72,73] Having observed substantial heterogeneity for most strata, we applied the random-effects model to synthesize study effects using the restricted maximum likelihood method to estimate between-study variance.

To identify potential study heterogeneity, we performed univariate random-effects meta-regression analysis of various study-level continuous characteristics: (1) mean age, (2) sex proportion, (3) diabetes prevalence, and (4) follow-up duration. We chose

these variables because they were most frequently reported and adjusted for across existing studies. In addition to meta-regression, we also conducted subgroup analysis on a potentially effect-modifying vision-related categorical characteristic: presenting versus best-corrected VA. Presenting VA is measured with participants wearing their habitual optical correction, whereas best-corrected VA is measured after correcting for any refractive errors identified.[74]

Subgroups analyses on other vision-related characteristics, including VA versus VF, monocular versus binocular, and near versus distance, were not performed because of insufficient data. The sensitivity of our overall results to the exclusion of unadjusted estimates also was examined. Finally, we assessed funnel-plot asymmetry both visually and using Egger's bias test. Where publication bias was suspected, we used the trim-and-fill method to re-estimate the pooled OR after imputing studies that potentially were missing. Final pooled ORs were reported with 95% confidence intervals (CIs) and we considered a 2-sided *P* value of less than 0.05 as statistically significant. A meta-analysis of the association between CIM and VI was not conducted because of insufficient data on OR from the published reports. Among the 9 studies analyzing the association between CIM and VI, only 2 reported ORs. The other 7 studies reported estimates of linear regression, which were not suitable for our meta-analysis. All analyses were conducted using Stata software version 16.0 (Stata Corp). The systematic review protocol is reported in the Appendix 3 (available at www.aaojournal.org).

Results

A total of 2172 nonduplicated abstracts were identified from the systematic search. In addition, 2 studies (1 cross-sectional and 1 cohort) that were in press but not yet listed electronically were provided by coauthors. The titles and abstracts of the 2174 articles were screened, of which 160 full-text articles were retrieved (Fig 1). Forty-three articles subsequently were accepted according to our inclusion criteria (28 cross-sectional, 14 cohort, and 1 case-control studies).

Of the 28 cross-sectional articles, most (90%) reported moderate to high NOS scores, with 15 graded as high quality (≥8 stars) and 10 graded as moderate quality (5−7 stars). The remaining 3 studies were classified as poor quality (0−4 stars). Of the 14 cohort studies, 100% reported moderate to high NOS scores, with 12 graded as high quality and 2 graded as moderate quality. The case-control study was graded as moderate quality. The 3 articles classified as poor quality were excluded, leaving 40 articles for inclusion (Table S1, available at www.aaojournal.org).

Study Characteristics

The characteristics of the 40 included studies are summarized in Tables S2 and S3 (available at www.aaojournal.org). In total, 31 studies (17 cross-sectional, 13 cohort, and 1 case-control studies) investigated the relationship between VI (exposure) and CIM (outcome), 6 cross-sectional studies investigated this relationship in the other direction, and 3 studies (2 cross-sectional and 1 cohort) investigated the relationship of VI and CIM bidirectionally. The total number of participants was 47 913 570; 9 and 31 studies reported on Asian and White populations, respectively. Among the 40 studies in this systematic review, 31 had adequate data to be included in the meta-analyses (Fig 1), whereas 9 were excluded because ORs or frequency counts of individuals with VI and CIM were unavailable. The total number of participants included in our meta-analysis was 47 907 988.

Evaluation of Visual Impairment

Of the 36 studies reporting VA measurements, 26 used distance VA only (e.g., Early Treatment Diabetic Retinopathy Study chart), 5 used near VA only (e.g., Rosenbaum Pocket vision screener), and 5 reported both distance and near VA. Most (n = 18) either defined VI as VA worse than 20/40 or 0.3 logarithm of the minimum angle of resolution or reported VA continuously (n = 9). Other definitions of VI are listed in Tables S2 and S3 (available at www.aaojournal.org). Of the 7 studies using VF measures (e.g., Humphrey perimetry), 2 defined VI as VF of 10° or less in radius around central fixation.[43,45] The other 5 studies used various other definitions of VF (Tables S2 and S3, available at www.aaojournal.org).[24,25,44,53,69]

Evaluation of Cognitive Impairment

Among studies reporting cognitive screening, 12 used the MMSE, of which 5 reported MMSE scores continuously,[27,34,37,40,57] whereas 7 defined CIM using various cut-offs (Tables S2 and S3, available at www.aaojournal.org).[27,28,31,32,38,39,42,49] The other 16 studies used other validated cognitive screening tests (Tables S2 and S3). Twelve studies reported diagnostic evaluation of CIM, of which 8 reported the prevalence or incidence of MCI or dementia.[36,43,45,47,53,55,59,61] Other definitions of CIM are listed in Tables S2 and S3. The diagnostic procedures were performed according to Petersen,[65] the Diagnostic and Statistical Manual of Mental Disorders IV,[66] National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association,[67] and International Classification of Diseases, Ninth or Tenth Revision, criteria.[75]

Cross-Sectional Association between Visual Impairment and Cognitive Impairment

Outcome: Cognitive Screening Tests. Fourteen cross-sectional studies explored the association between VI and CIM measured using screening tests and the findings were equivocal, with 7 studies[27,32,33,35,38,41,42] and 5 studies[24,29,34,39,44] showing a significant and nonsignificant relationship, respectively; and 2 studies[30,31] were inconclusive (Table S2, available at www.aaojournal.org).

Outcome: Clinical Diagnosis. All 4 cross-sectional studies[36,43,45,47] that defined CIM using diagnostic evaluation showed a significant association between VI and CIM. For example, the Sydney Memory and Aging Study found that participants with better VA showed a smaller odds of MCI as compared with those with poorer VA (OR, 0.39; 95% CI, 0.18−0.86; n = 757).[36] The only

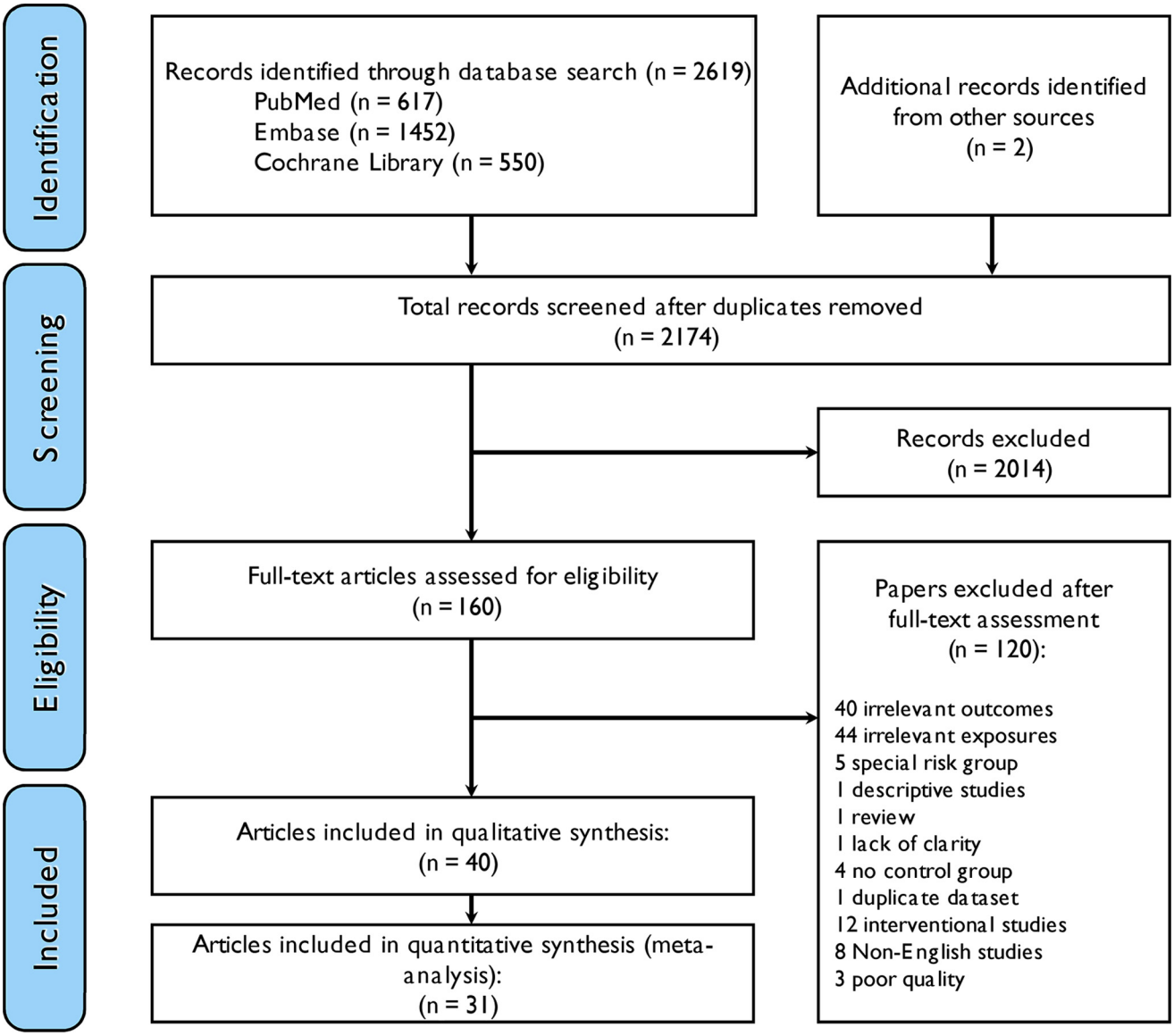

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses flow diagram showing the study selection process.

case-control study[48] reported an inconclusive result (Table S2, available at www.aaojournal.org).

Meta-Analyses, Meta-Regression, and Publication Bias. Pooling the above estimates (Fig 2; Table S4, available at www.aaojournal.org) showed that VI was associated with significantly higher odds of: (1) any CIM (pooled OR, 2.38; 95% CI, 1.84−3.07; $P < 0.001$; $I^2 = 65.3\%$; n = 29 015);and (2) clinically diagnosed dementia (pooled OR, 2.43; 95% CI, 1.48−4.01; $P < 0.001$; $I^2 = 91.4\%$; n = 47 834 144). The ORs remained significant after excluding unadjusted estimates (Table S5, available at www.aaojournal.org). A sensitivity analysis performed by excluding results of the study conducted by Hamedani et al[45] (n = 47 582 342) showed that the association between VI and clinically diagnosed dementia remained statistically significant (data not shown).

In the subgroup meta-analyses stratified by type of VI (Table S6, available at www.aaojournal.org), the association between presenting VI (pooled OR, 2.00; 95% CI, 1.60−2.51; $P < 0.001$) or best-corrected VI (pooled OR, 3.07; 95% CI, 2.03−4.67; $P < 0.001$) and any CIM did not differ significantly ($P = 0.080$ for interaction). Subgroup meta-analyses stratified by definition of VI worse than 20/40 or other definitions showed that the associations between different definitions of VI and any CIM did not differ significantly (data not shown). Similarly, subgroup meta-analyses stratified by types of screening tests, MMSE or other measures, showed that the associations between VI and different types of any CIM measures did not differ significantly (data not shown). In the meta-regression analyses (Table S7, available at www.aaojournal.org), age, sex, and diabetes status did not modify effect sizes significantly.

Egger's bias test did not find any significant funnel plot asymmetry (Table S4, available at www.aaojournal.org).

Longitudinal Association between Visual Impairment and Cognitive Impairment

Outcome: Cognitive Screening Tests. Of the 9 longitudinal studies that measured CIM using screening tests, 5 studies[49,50,57,60,62] and 3 studies[52,56,58] showed a significant and nonsignificant relationship, respectively; and 1 study[59] was inconclusive (Table S2, available at www.aaojournal.org).

Outcome: Clinical Diagnosis. Of the 5 longitudinal studies that diagnostically defined CIM, 4 studies[53–55,61] showed a significant association between VI and CIM, whereas 1 study[59] was inconclusive (Table S2). For example, Sachdev et al[54] found that the reversion from MCI to normal cognitive function was more likely for participants with better vision (OR, 9.35; 95% CI, 1.55–55.86; n = 223) in the Sydney Memory and Aging Study.

Meta-Analyses, Meta-Regression, and Publication Bias. Pooling the above estimates (Fig 3) showed that VI significantly predicted the odds of: (1) any CIM (pooled OR, 1.66; 95% CI, 1.46–1.89; $P < 0.001$; $I^2 = 11.0\%$; n = 14 912) and (2) clinically diagnosed dementia (pooled OR, 2.09; 95% CI, 1.37–3.21; $P = 0.001$; $I^2 = 78.8\%$; n = 26 132). The ORs remained significant after excluding unadjusted estimates (Table S5, available at www.aaojournal.org).

In the meta-regression analyses (Table S7, available at www.aaojournal.org), longer follow-up time was associated with significantly smaller reported ORs for studies evaluating longitudinal associations between VI and any CIM (relative OR, 0.94; 95% CI, 0.89–1.00; $P = 0.037$) and between VI and dementia (relative OR, 0.91; 95% CI, 0.84–0.98; $P = 0.018$). Moreover, for the longitudinal association between VI and dementia, studies with increasing age (relative OR, 1.19; 95% CI, 1.08–1.31; $P < 0.001$) and lower proportions of male participants (relative OR, 0.93; 95% CI, 0.89–0.97; $P = 0.001$) reported significantly larger ORs. No other significant effect modifiers were found. For the longitudinal association between VI and any CIM, although Egger's bias found significant funnel plot asymmetry ($P = 0.038$), the trim-and-fill method returned an unchanged pooled OR (Table S4; Fig S4, available at www.aaojournal.org).

Cross-Sectional Association between Cognitive Impairment and Visual Impairment: Systematic Review Findings Only

Exposure: Cognitive Screening Tests. Six cross-sectional studies using cognitive screening tests reported a significant association between CIM and VI (Table S3, available at www.aaojournal.org). In the Singapore Epidemiology of Eye Disease study, CIM was associated independently with higher odds of presenting VI (OR, 2.15; 95% CI, 1.75–2.63; n = 4064) and best-corrected VI (OR, 2.07; 95% CI, 1.60–2.68; n = 4064).[46]

Exposure: Clinical Diagnosis. Of the 2 studies that defined CIM using diagnostic evaluation (both univariate analyses only; NOS score, 5), Trick et al[25] showed that, relative to control participants, VF parameters were reduced significantly in senile dementia of Alzheimer type ($P = 0.003$ for foveal sensitivity, $P = 0.006$ for mean deviation, and $P = 0.041$ for corrected pattern standard deviation). In contrast, Rizzo et al[26] did not find any significant differences in either near or distance vision between Alzheimer's disease patients and control participants.

Longitudinal Association between Cognitive Impairment and Visual Impairment: Systematic Review Findings Only

Only 1 cohort study evaluated the longitudinal relationship between CIM and VI. Using 4 waves of longitudinal data collection in the Salisbury Eye Evaluation study, Zheng et al[57] reported that worse MMSE scores in the previous wave were associated with worse VA in the subsequent wave ($\beta = -0.003$; $P < 0.001$; n = 2520).

Discussion

In our systematic review and meta-analyses, we found evidence for a directional link between VI and CIM, with VI being associated with an approximately 2-fold increased odds of prevalent or incident CIM. Our systematic review also suggested a reverse directional link, with CIM being associated with increased odds of VI; however, too few studies were available to conduct a formal meta-analysis, so this finding should be interpreted with caution. Overall, evidence suggests that VI is a potential risk factor of CIM, although further work is needed to confirm the reverse association. Our results suggest that vision screening and timely treatment strategies beginning in middle age (i.e., ≥40 years) may be appropriate risk-reduction approaches for CIM, and these interventions may be considered by healthcare professionals, researchers, and policymakers.

Our finding that VI is predictive of cognitive decline adds to previous systematic reviews and meta-analyses suggesting that sensory impairments, including hearing and olfactory deficits, are risk factors of CIM.[76,77] A recently published summary of dementia prevention, intervention, and care outlined 12 risk factors for CIM that accounted for an estimated 40% of all cases of dementia.[78] This information thus suggests that the other 60% risk of CIM has not been well elucidated in the literature. Our results suggest that VI may be a potential risk factor that may help to explain at least some of the gaps in the aforementioned risk of CIM.

Several pathways may explain our finding of VI as a risk factor of CIM. First, a loss of visual sensory information may lead to cortical atrophy and subsequent neural reorganization,[16,79] as evidenced by neuroimaging and pathologic analysis.[13] Alternatively, degraded and impaired visual input may result in errors in perceptual processing, with consequent decline in higher-order cognitive performance.[80] Visual impairment also may lead to cognitive decline indirectly by limiting the

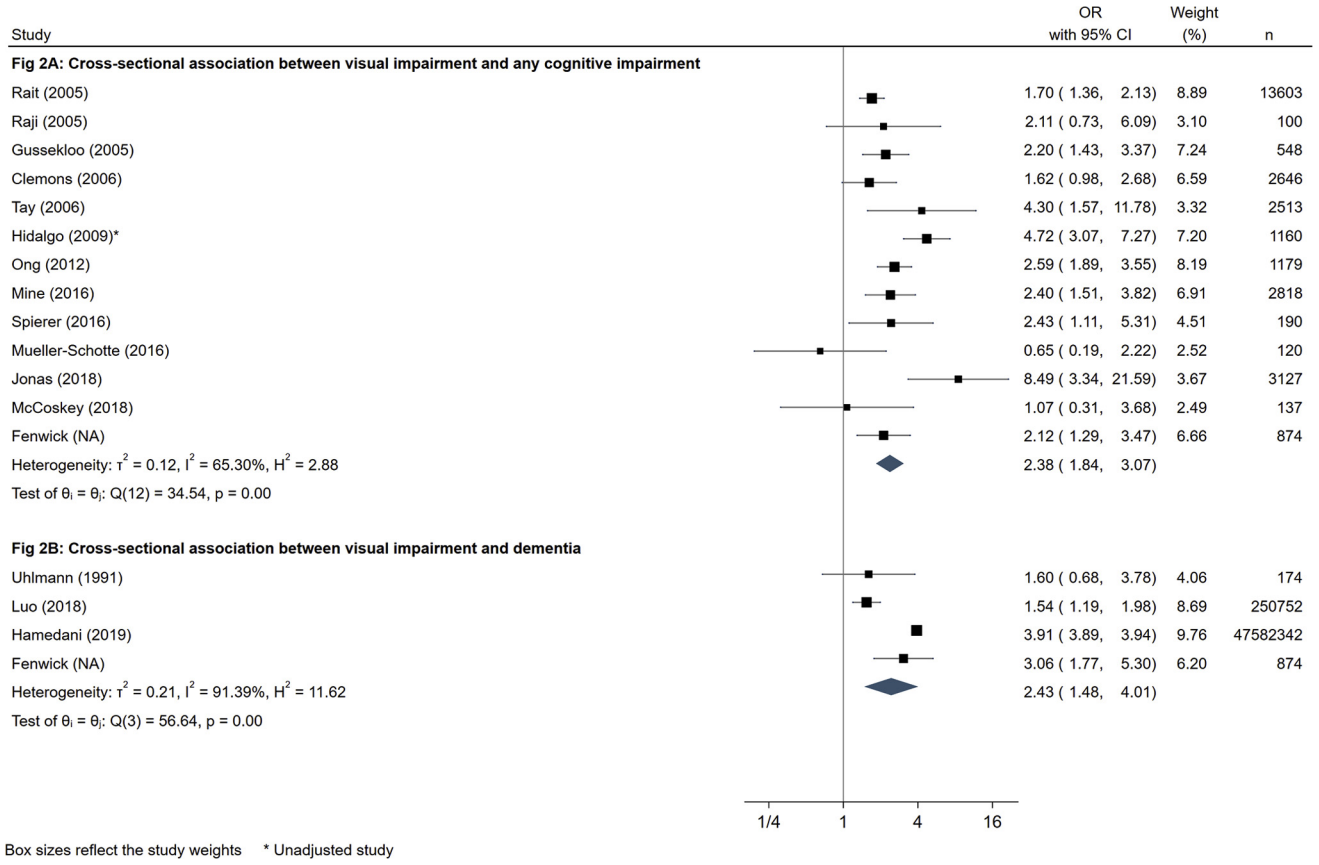

Figure 2. Random-effect meta-analyses of the cross-sectional association between visual impairment and cognitive impairment. Blue diamonds are the estimated pooled odds ratio (OR) for each meta-analysis; box sizes reflect the relative weight apportioned to studies in the meta-analysis. CI = confidence interval.

interactive experience of individuals within the environment, resulting in social isolation and restricted participation in mentally stimulating activities.[54,78,81] Finally, many age-related eye diseases (e.g., age-related macular degeneration [AMD], glaucoma, diabetic retinopathy) associated with VI also have been linked with CIM and dementia.[82–84] For example, AMD and Alzheimer's disease have been found to share many risk factors and pathophysiologic processes. For instance, the ε4 ApoE allele, a prevalent genetic risk factor of Alzheimer's disease, also is associated with higher risk of AMD.[85] Moreover, β-amyloid deposition, a common histopathologic feature in the brain of Alzheimer's patients, also has been reported to be present in drusen and retinal pigment epithelium of patients with AMD.[86] Similarly, β-amyloid aggregation may result in dysfunctional mitochondrial, inflammatory, and vascular regulation, potentially leading to both VI and CIM.[87] Further work is needed to investigate whether vision-saving interventions could prevent or delay the progression, or even partially reverse CIM.

Interestingly, our meta-regression finding of an attenuated longitudinal relationship between VI and CIM with longer follow-up time suggests that cognitive and psychological adaptation developed over time by patients to cope with VI-imposed restrictions, for example, engaging in cognitively stimulating activities and seeking more social support,[88] may reverse VI-induced cognitive decline. Our meta-regression also revealed higher odds of a longitudinal association between VI and CIM with increasing proportion of women. This may be explained by previous studies reporting that psychosocial factors and adaptation were more important for women.[89] Future clinical trials also could evaluate the efficacy of community-based interventions, focused on encouraging people with VI to participate in physical, mental, and social activities, to improve cognition.

In addition, our meta-regression result of stronger longitudinal associations between VI and CIM (i.e., higher odds) with increasing age suggest the possibility of a shared underlying cause, that is, the common-cause hypothesis, in which both VI and CIM are mediated through shared underlying pathobiological processes,[16] for example, accumulation of amyloid proteins, increased oxidative stress, and increased prevalence of vascular diseases.[17] Previous studies also have shown relationship between retinal microvascular and neuronal changes in patients with CIM or dementia.[14,15]

We found a potential link between CIM and increased risk of VI. It is possible that the additional cognitive

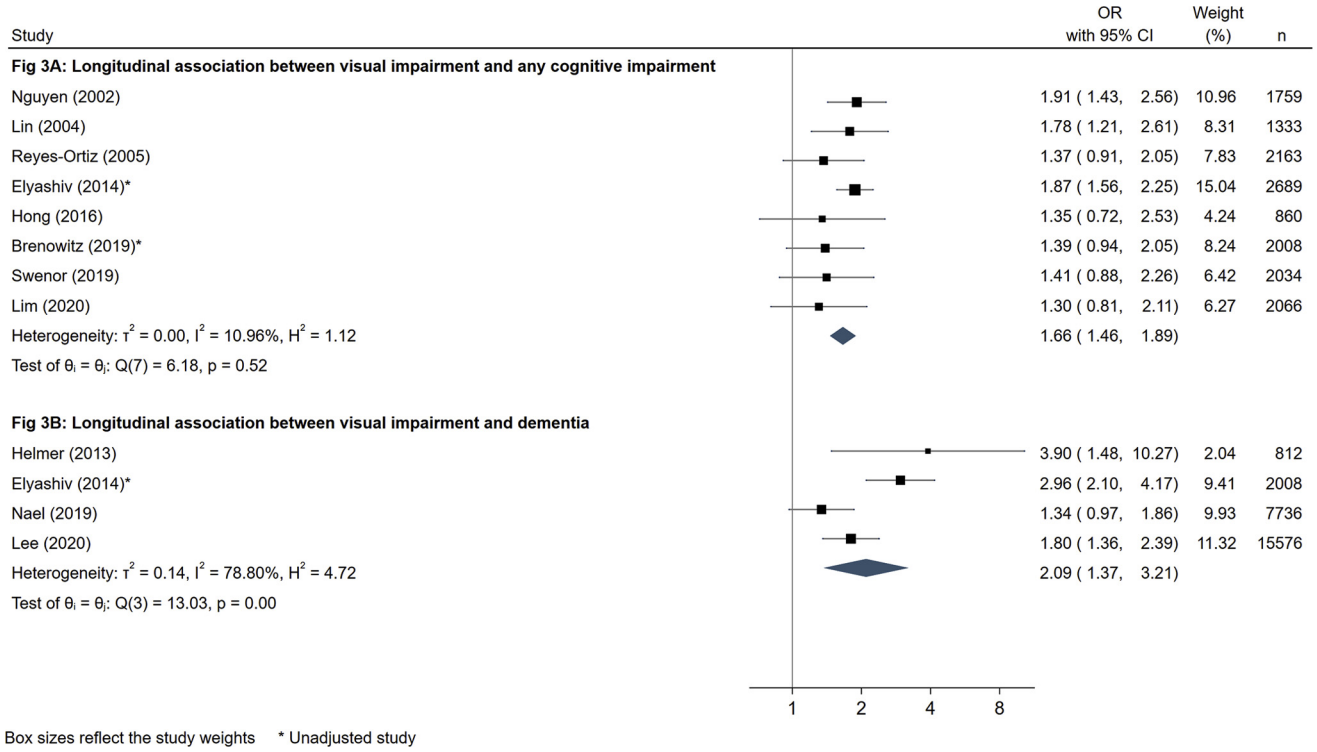

Figure 3. Random-effect meta-analyses of the longitudinal association between visual impairment and cognitive impairment. Blue diamonds are the estimated pooled odds ratio (OR) for each meta-analysis; box sizes reflect the relative weight apportioned to studies in the meta-analysis. CI = confidence interval.

resources allocated to sensory processing to overcome impaired visual input may end up depleting cognitive capacities for other tasks.[16,90] Alternatively, cognitively impaired patients also may encounter more challenges in seeking medical help and managing treatment for VI.[91] For instance, patients living in long-term care facilities may not use their glasses frequently or may wear inaccurate glasses.[92] Moreover, caregivers may not want to subject

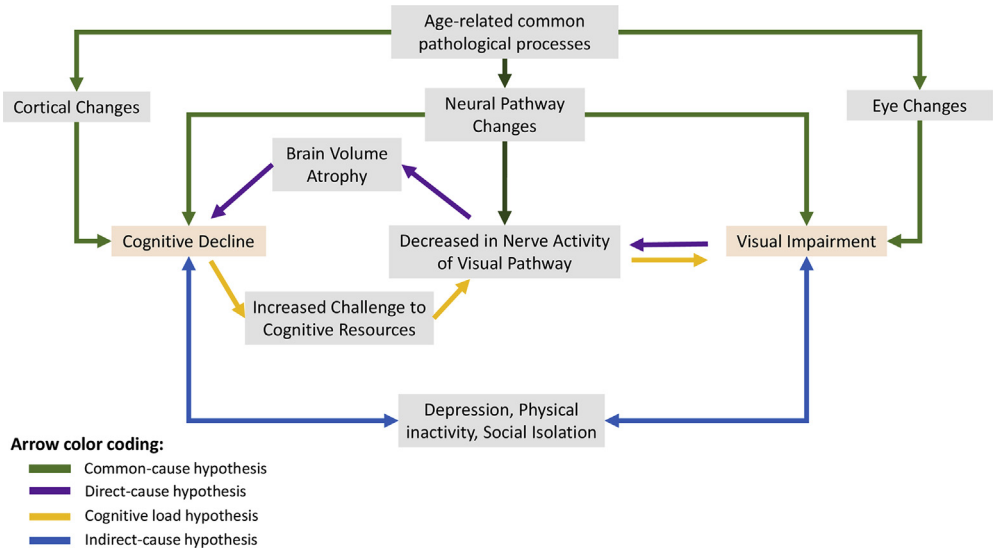

Figure 5. Diagram showing a framework of potential mechanisms explaining the bidirectional relationship between visual impairment and cognitive impairment. The purple pathway represents the direct-cause hypothesis, in which impoverished visual input secondary to visual impairment leads to decreased nerve activity of the visual pathway. This cascade leads to neuropathologic and structural changes such as brain volume atrophy, thereby resulting in cognitive impairment.

dementia patients to excessive surgical and medical consultations relating to comorbid conditions.[92] In addition, physicians also may misattribute visual disturbances to the underlying cognitive deficits of patients with CIM, and thus overlook visual comorbidities.[93] However, our review identified a lack of high-quality epidemiologic studies, especially those reporting clinical diagnosis of dementia, that examined this reverse causality relationship. Thus, more comprehensive longitudinal studies are needed to evaluate this relationship further.

Ultimately, it is likely that multiple mechanisms underlie this bidirectional association between vision and cognition (Fig 5), potentially resulting in a vicious cycle of both visual and cognitive deterioration. Thus, future studies should focus on investigating the bidirectional link and factors underpinning the relationship between VI and CIM.

Strengths and Limitations

The strengths of our study include a large and diverse pool of individuals, making our findings generalizable to the global population, and the application of a rigorous protocol of systematic searching, quality grading, and bias assessment according to internationally accepted guidelines. Furthermore, we included only validated measures of VI and CIM and conducted subgroup meta-analyses and meta-regression to ensure the robustness of our findings.

Nevertheless, some study limitations must be acknowledged. First, the meta-analysis was limited to English-language publications using standardized definitions of CIM only, which may have excluded potentially relevant articles in other languages. Second, because of limited data, we were unable to synthesize the association between VI and MCI, the severity of VI, and the relationship between CIM and VI in meta-analyses. Third, we did not include studies examining the associations between different ocular diseases and causes of CIM. This reduces our ability to elucidate the mechanisms underlying the specific relationships between these conditions. We also did not consider other components of vision (e.g., contrast sensitivity, stereoacuity, color vision, and visual hallucination) or specific eye diseases or CIM pathologic features that may reduce the capacity to detect further association between the visual function system and CIM. For example, apart from VA and VF, Alzheimer's disease also has been linked to deficits in color vision,[94] contrast sensitivity,[94] stereoacuity,[94] and other complex visual problems, such as difficulties in reading words,[95] challenges in finding objects,[96] and problems in object and shape recognition.[97] In contrast, visual hallucination is a more prominent symptom of Lewy body dementia and Parkinson's disease dementia.[98]

In addition, the moderate to high heterogeneity in our meta-analyses (only partially explained by our meta-regression analyses) indicated that other unconsidered sources potentially may contribute to the varying outcomes among studies. Moreover, although hazard ratios may be a better measurement than ORs to account for the loss of follow-up in longitudinal studies, we chose to meta-analyze OR because it was the most frequently reported statistical estimate of effect across studies. Finally, our results may not have accounted for the possibility of overdiagnosis, underdiagnosis, or misdiagnosis of CIM as a result of challenges that visually impaired individuals encounter when performing screening tests.[27,56] Future research, using more stringent diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders V and National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria of CIM, should be used.

In summary, our findings suggest that VI is a potential risk factor of CIM, although further work is needed to confirm the association of CIM as a risk factor of VI. Our findings provide additional information for the development of clinical guidelines and policies on the prevention and management of VI in the cognitively impaired population and of CIM in visually impaired patients. Future prospective studies and randomized controlled trials are needed to investigate whether CIM predicts the risk of VI and whether, in cognitively impaired patients, vision-saving interventions are effective in preventing the progression of cognitive decline.

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Footnotes and Disclosures

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CI** = confidence interval; **CIM** = cognitive impairment; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental Status Examination; **NOS** = Newcastle-Ottawa scale; **OR** = odds ratio; **VA** = visual acuity; **VF** = visual field; **VI** = visual impairment.

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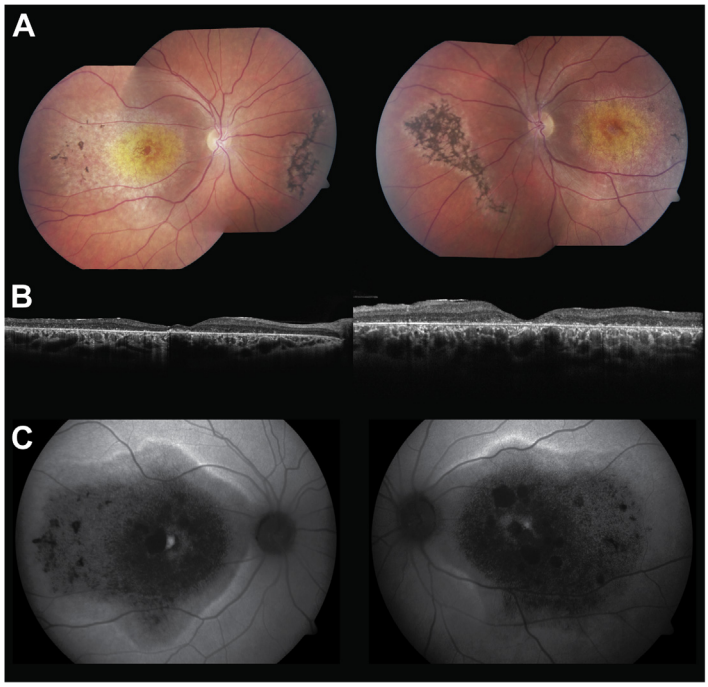
Pictures & Perspectives



Retinopathy of Transcobalamin II Deficiency: Long-Term Stability with Treatment

A French-Canadian girl with megaloblastic anemia detected at age 17 months received oral vitamin B12 and folate, with hematological improvement. At age 13, additional retinopathy with macular atrophy, peripheral neuropathy, and elevated homocysteine and methylmalonate levels led to the diagnosis of congenital transcobalamin II deficiency (TCN2 mutations c.548_549dupTG(p.Glu184Tryfsx24) and c.940G>A(p.Val314Ile)). Visual acuity was 20/40 in the right eye and 20/50 in the left eye with bilateral central-sparing central field defects. Weekly intramuscular hydroxycobalamin was begun. Twenty-one years later, her supplementation continues, and ocular findings remain stable. Fundus photos (Fig **A**), OCT (Fig **B**), and autofluorescence (Fig **C**, showing diffuse mottled macular hypofluorescence surrounded by hyperfluorescent lesion border) at age 34 years are shown (Magnified version of Fig **A**-**C** is available online at www.aaojournal.org).

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