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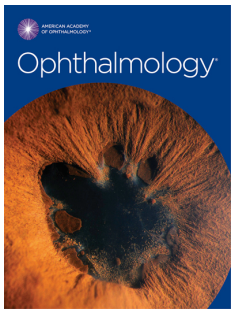

THE BIDIRECTIONAL RELATIONSHIP BETWEEN VISION AND COGNITION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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THE BIDIRECTIONAL RELATIONSHIP BETWEEN VISION AND COGNITION:

A SYSTEMATIC REVIEW AND META-ANALYSIS

Running Head: Vision Impairment and Cognitive Impairment

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Abbreviations and Acronyms:

VI = Visual impairment

CIM = Cognitive impairment

CI = Confidence interval

OR = Odds ratio

PICOS = Population-Intervention-Comparison-Outcome-Study Design

PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analyses

MCI = Mild cognitive impairment

VA = visual acuity

VF = visual field

ETDRS = Early Treatment Diabetic Retinopathy Study

ICD = International Classification of Diseases

MMSE = Mini Mental Status Examination

MoCA = Montreal Cognitive Assessment

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders-IV

NINCDC-ADRDA = National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association

STROBE = Strengthening the Reporting of Observational Studies in Epidemiology

NOS = Newcastle-Ottawa Scale

AMD = Age-related Macular Degeneration

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ABSTRACT

Topic: Visual impairment (VI) and cognitive impairment (CIM) are prevalent age-related conditions that impose substantial burden on the society. While the bidirectional association of VI and CIM has been hypothesized, findings have been equivocal. Hence, we conduct a systematic review and meta-analysis to examine the bidirectional relationship between VI and CIM.

Clinical Relevance: 60% risk of CIM has not been well-elucidated in the literature. A bidirectional relationship between CIM and VI may provide opportunities for developing public health strategies for early detection and management of risk factors for both VI and CIM in older people.

Methods: Pubmed, Embase and Cochrane Central registers were systematically searched for observational studies, published from inception until 6 April 2020, in adults aged ≥ 40 years 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 (OR), and 95% confidence interval (CI). Publication bias and heterogeneity were examined using Egger's test, meta-regression, and trim-and-fill methods.

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 [OR (95%CI)] of: (i) any CIM [cross-sectional: 2.38 (1.84-3.07); longitudinal: 1.66 (1.46-1.89)], and (ii) clinically diagnosed dementia [(cross-sectional: 2.43 (1.48-4.01); longitudinal: 2.09 (1.37-3.21)], compared to persons without VI. Significant heterogeneity was partially explained by differences in age, sex and follow-up duration. There was also some evidence that individuals with CIM, relative to cognitively intact persons, were more likely to have VI, with most papers (8/9, 89%) reporting significantly positive associations, however meta-analyses on this association could not be conducted due to insufficient data.

Conclusions: Overall, our work suggests that VI is a risk factor of CIM while further work is needed to confirm the association of CIM as a risk factor for VI. Strategies for early detection and management of both visual and cognitive impairment in older people may minimize individual clinical and public health consequences.

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INTRODUCTION

With 2 billion people estimated to be aged ≥ 60 years worldwide by 2050,[1] the number of individuals with cognitive impairment (CIM) is also 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] There is limited treatment strategies for CIM or dementia.[6] Therefore, identifying potentially modifiable risk factors for CIM and instituting community risk-reduction strategies may be a better strategy than pharmaceutical approaches at reducing the burden of disease.[7-9]

Visual impairment (VI) is also an age-related condition and estimated to affect over 1 billion individuals by 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,[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 due to heterogeneity in research methodologies. Moreover, while 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 critically examine the bidirectional associations between VI and CIM. We hypothesize 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 6 April 2020. The core keywords included "Visual Impairment" AND "Cognitive Impairment" AND "Adult". Subsequently, filters such as "publication type" and "human" were added to narrow down 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 (PRISMA) 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-Outcome-Study Design (PICOS) framework in the PRISMA guidelines. Since the pathophysiologic processes of Alzheimer's disease may begin 10-20 years before the onset of Alzheimer dementia and this may present as mild CIM (MCI),[63-65] middle-aged (40-64 years) and older adults (≥65 years) 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 VI according to visual acuity (VA) or visual field (VF) losses, assessed by objective measurements (e.g. Snellen chart, Early Treatment Diabetic Retinopathy (ETDRS) chart, Humphrey perimeter), in agreement with the International Classification of Diseases 11th Revision (ICD-

11) criteria of VI and blindness. CIM was defined as any CIM assessed using clinically validated cognitive screening tests (e.g. Mini Mental Status Examination (MMSE) and Montreal Cognitive Assessment (MoCA)); diagnostic evaluation based on pre-defined diagnostic criteria (e.g. Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV);[66] or National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDC-ADRDA)[67]).

The inclusion criteria therefore consisted of (1) adults aged ≥40 years, (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, (3) case reports, case series, and conference abstracts, (4) animal and in-vitro or in-vivo, (5) interventional, (6) non-English, (7) no clear definitions of the exposure or outcome variables as per our inclusion criteria, (8) special risk groups (e.g. people with diabetes, cancer patients, patients with Down's syndrome), and (9) 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 (TAV and BKJT) assessed the titles and abstracts of our 2174 identified papers independently according to the predefined inclusion and exclusion criteria. If there was insufficient information within the abstract, the full-text articles of relevant studies were extracted for further evaluation. If consensus could not be reached, three other co-authors (EKF, REKM and PG) were consulted for arbitration.

Data extraction was performed by the first author (TAV) and checked for accuracy by co-authors (BKJT and ATLG). Data were extracted from each article based on the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) 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 (TAV and BKJT) 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 10 for cross-sectional and 9 for prospective and case-control studies.[71]

DATA SYNTHESIS AND ANALYSIS

Statistical analysis was performed by ATLG and reviewed by TAV. 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. As too few papers reported on the cross-sectional or longitudinal VI-MCI relationship, they were excluded from meta-analyses. We chose to meta-analyze odds ratios (OR) as 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 <0.10 or if the I^2 statistic was ≥50%.[72,73] Having observed substantial heterogeneity for the majority of 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 univariable 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. Presenting VA is measured with participants wearing their habitual

optical correction while 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 vs binocular, and near vs distance were not performed due to insufficient data. The sensitivity of our overall results to the exclusion of unadjusted estimates was also examined. Lastly, 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 were potentially missing. Final pooled ORs were reported with 95% confidence intervals (CI) and we considered a 2-sided P-value <0.05 as statistically significant. A meta-analysis of the association between CIM and VI was not conducted due to 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, version 16.0. The systematic review protocol is reported in the **Appendix 3** (available at www.aaojournal.org).

RESULTS

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

Of the 28 cross-sectional papers, the majority (90%) had moderate to high NOS scores, with 15 graded as 'high quality' (≥ 8 stars) and 10 as 'moderate quality' (5-7 stars). The remaining 3 studies were classified as 'poor quality' (0-4 stars). Of the 14 cohort studies, 100% had moderate to high NOS score,

with 12 graded as 'high quality' and 2 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 1,** available at www.aaojournal.org).

STUDY CHARACTERISTICS

The characteristics of the 40 included studies are summarized in **Tables 2 and 3** (available at www.aaojournal.org). In total, 31 (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 (2 cross-sectional and 1 cohort) studies investigated the relationship of VI and CIM bidirectionally. The total number of participants was 47,913,570; and 9 and 31 studies reported on Asian and Caucasian populations, respectively.

Among the 40 studies in our systematic review, 31 had adequate data to be included in our meta-analyses (**Fig 1**), while 9 were excluded as 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 VI

Of the 36 studies reporting VA measures, 26 used distance VA (e.g.: ETDRS chart) only, 5 used near VA (e.g.: Rosenbaum Pocket vision screener) only, and 5 reported both distance and near VA. Most (N=18) either defined VI as VA < 20/40 or 0.3 LogMAR or reported VA continuously (N=9). Other definitions of VI are listed in **Tables 2 and 3** (available at www.aaojournal.org).

Of the 7 studies using VF measures (e.g.: Humphrey perimetry), 2 defined VI as VF $\leq 10°$ in radius around central fixation.[43,45] The other 5 studies used various other definitions of VF (**Tables 2 and 3**, available at www.aaojournal.org).[24,25,44,53,69]

EVALUATION OF COGNITIVE IMPAIRMENT (CIM)

Among studies reporting cognitive screening, 12 used the MMSE, of which 5 reported MMSE scores continuously[27,34,37,40,57] while 7 defined CIM using various cut-offs (**Tables 2 and 3**, available at www.aaojournal.org).[27,28,31,32,38,39,42,49] The other 16 studies utilized other validated cognitive screening tests (**Tables 2 and 3**, available at www.aaojournal.org).

12 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 2 and 3** (available at www.aaojournal.org). The diagnostic procedures were performed according to Petersen,[65] DSM-IV,[66] NINCDS-ADRDA,[67] ICD-9 or ICD-10 criteria.[75]

CROSS-SECTIONAL ASSOCIATION BETWEEN VI AND CIM

Outcome: Cognitive screening tests

Fourteen cross-sectional studies explored the association between VI and CIM measured using screening tests and findings were equivocal, with 7[27,32,33,35,38,41,42] and 5[24,29,34,39,44] studies showing a significant and non-significant relationship, respectively; and 2[30,31] were inconclusive (**Table 2**, 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 had smaller odds of MCI as compared to those with poorer VA (OR=0.39, 95%CI=0.18-0.86, N=757).[36] The only case-control study[48] reported an inconclusive result (**Table 2**, available at www.aaojournal.org).

Meta-Analyses, Meta-Regression and Publication Bias

Pooling the above estimates (**Fig 2 and Table 4**, available at www.aaojournal.org) showed that VI was associated with significantly higher odds of: (i) any CIM (pooled OR=2.38, 95%CI=1.84-3.07, $p<0.001$, $I^2=65.3\%$, N=29,015); and (ii) 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 5**, available at www.aaojournal.org). A sensitivity analysis performed by excluding result of the study conducted by Hamedani and colleagues (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 6**, available at www.aaojournal.org), the association between presenting (pooled OR=2.00, 95%CI=1.60-2.51, p<0.001) or best-corrected (pooled OR=3.07, 95%CI=2.03-4.67, p<0.001) VI, and any CIM did not differ significantly (p for interaction=0.080). Subgroup meta-analyses stratified by definition of VI, < 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 7**, available at www.aaojournal.org), age, sex, and diabetes did not significantly modify effect sizes. Egger's bias test did not find any significant funnel plot asymmetry (**Table 4**, available at www.aaojournal.org).

LONGITUDINAL ASSOCIATION BETWEEN VI AND CIM

Outcome: Cognitive screening tests

Of the 9 longitudinal studies that measured CIM using screening tests, 5[49,50,57,60,62] and 3[52,56,58] showed a significant and non-significant relationship, respectively; and 1[59] was inconclusive (**Table 2**, available at www.aaojournal.org).

Outcome: Clinical diagnosis

Of the 5 longitudinal studies that diagnostically defined CIM, 4[53-55,61] showed a significant association between VI and CIM while 1[59] was inconclusive (**Table 2**, available at www.aaojournal.org). For example, Sachdev and colleagues 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.[54]

Meta-Analyses, Meta-Regression and Publication Bias

Pooling the above estimates (**Fig 3**) showed that VI significantly predicted the odds of: (i) any CIM (pooled OR=1.66, 95%CI=1.46-1.89, p<0.001, I^2=11.0%, N=14,912); and (ii) 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 5**, available at www.aaojournal.org).

In the meta-regression analyses (**Table 7**, 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 proportion of male (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, while Egger's bias found significant funnel plot asymmetry (p=0.038), the trim-and-fill method returned an unchanged pooled OR (**Table 4 and Fig 4,** available at www.aaojournal.org).

CROSS SECTIONAL ASSOCIATION BETWEEN CIM AND VI – 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 3**, available at www.aaojournal.org). In the Singapore Epidemiology of Eye Study (SEED) study, CIM was independently associated with higher odds of presenting (OR=2.15, 95%CI=1.75-2.63, N=4064) and best corrected (OR=2.07, 95%CI=1.60-2.68, N=4064) VI.[46]

Exposure: Clinical diagnosis

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Of the 2 studies that defined CIM using diagnostic evaluation (both univariate analyses only, NOS=5), Trick and associates showed that, relative to controls, VF parameters were significantly reduced 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).[25] In contrast, Rizzo and colleagues did not find any significant differences in either near or distance vision between Alzheimer's cases and controls.[26]

LONGITUDINAL ASSOCIATION BETWEEN CI AND VI – 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 and colleagues reported that worse MMSE scores in the previous wave was associated with worse VA in the subsequent wave (β=-0.003; p<0.001, N=2520).[57]

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 two-fold increased odds of prevalent or incident CIM. Our systematic review also suggests a reverse directional link with CIM being associated with increased odds of VI; however, there were too few studies to conduct a formal meta-analysis, so this finding should be interpreted with caution. Overall, there is evidence that VI is a potential risk factor of CIM while 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 of 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, which 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 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 pathology.[13] Alternatively, degraded and impaired visual input may result in errors in perceptual processing, with consequent decline in higher-order cognitive performance.[80] VI may also lead to cognitive decline indirectly by limiting the interactive experience of individuals with 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 have also been linked with CIM and dementia.[82-84] For example, AMD and Alzheimer's disease have been found to share many risk factors and pathophysiological processes. For instance, ε4 ApoE allele, a prevalent genetic risk factor of Alzheimer's disease, also associated with higher risk of AMD.[85] Moreover, β-amyloid deposition, a common histopathological feature in the brain of Alzheimer's patients, has also 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 VI-CIM relationship with longer follow-up time suggests that cognitive and psychological adaptation developed over time by patients to cope with VI-imposed restrictions, e.g. engaging in cognitively stimulating activities and seeking more social support,[88] may reverse VI-induced cognitive decline. Our meta-regression also

285 revealed higher odds of longitudinal VI-CIM association with increasing proportion of female
286 participants. This may be explained by previous studies reporting that psychosocial factors and
287 adaptation were more important for women.[89] Future clinical trials could also evaluate the efficacy of
288 community-based interventions, focused on encouraging people with VI to participate in physical,
289 mental, and social activities, to improve cognition.

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

296 We found a potential link between CIM and increased risk of VI. It is possible that the additional
297 cognitive resources allocated to sensory processing to overcome impaired visual input may end up
298 depleting cognitive capacities for other tasks.[16,90] Alternatively, cognitively impaired patients may also
299 encounter more challenges in seeking medical help and managing treatment for their VI.[91] For instance,
300 patients living in long-term care facilities may not use their glasses frequently or may wear inaccurate
301 glasses.[92] Moreover, caregivers may not want to subject dementia patients to excessive surgical and
302 medical consultations relating to comorbid conditions.[92] In addition, physicians may also misattribute
303 visual disturbances to the underlying cognitive deficits of patients with CIM, and thus overlook visual
304 comorbidities.[93] However, our review identified a lack of high-quality epidemiological studies, especially
305 those reporting clinical diagnosis of dementia, that examined this reverse causality relationship. Thus,
306 more comprehensive longitudinal studies are needed to further evaluate this relationship.

307 Ultimately, it is likely that multiple mechanisms underlie this bidirectional association between
308 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 in order to ensure the robustness of our findings.

Nevertheless, some study limitations must be acknowledged. First, the meta-analysis was limited to English-language publications utilizing standardized definitions of CIM only, which may have excluded potentially relevant papers in other languages. Second, due to limited data, we were unable to synthesize the VI-MCI association, the severity of VI, and the CIM-VI relationship in meta-analyses. Third, we did not include studies examining the associations between different ocular pathologies and etiologies 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, stereo-acuity, color vision and visual hallucination), or specific eye diseases or CIM pathologies which may reduce the capacity to detect further association between the visual function system and CIM. For example, apart from visual acuity and visual field, Alzheimer's disease has also been linked to deficits in color vision,[94] contrast sensitivity,[94] stereo-acuity,[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, moderate to high heterogeneity in our meta-analyses (only partially explained by our meta-regression analyses) indicated that other unconsidered sources might potentially contribute to

the varying outcomes between studies. Moreover, although hazard ratios may be a better measurement than OR to account for the loss of follow-up in longitudinal studies, we chose to meta-analyze OR as it was the most frequently reported statistical estimate of effect across studies. Finally, our results may not accounted for the possibility of over-, under- or mis-diagnosis 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 DSM-5 and NINCDC-ADRDA criteria of CIM, should be utilized.

CONCLUSION

In summary, our findings suggest that VI is a potential risk factor of CIM while 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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LEGENDS FOR PRINT FIGURES:

Figure 1: PRISMA flow diagram showing the study selection process

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 for each meta-analysis; box sizes reflect the relative weight apportioned to studies in the meta-analysis

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

Figure 5: A framework of potential mechanisms explaining the bidirectional relationship between VI and cognitive impairment

As an illustration, 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 neuropathological and structural changes such as brain volume atrophy, thereby resulting in cognitive impairment.

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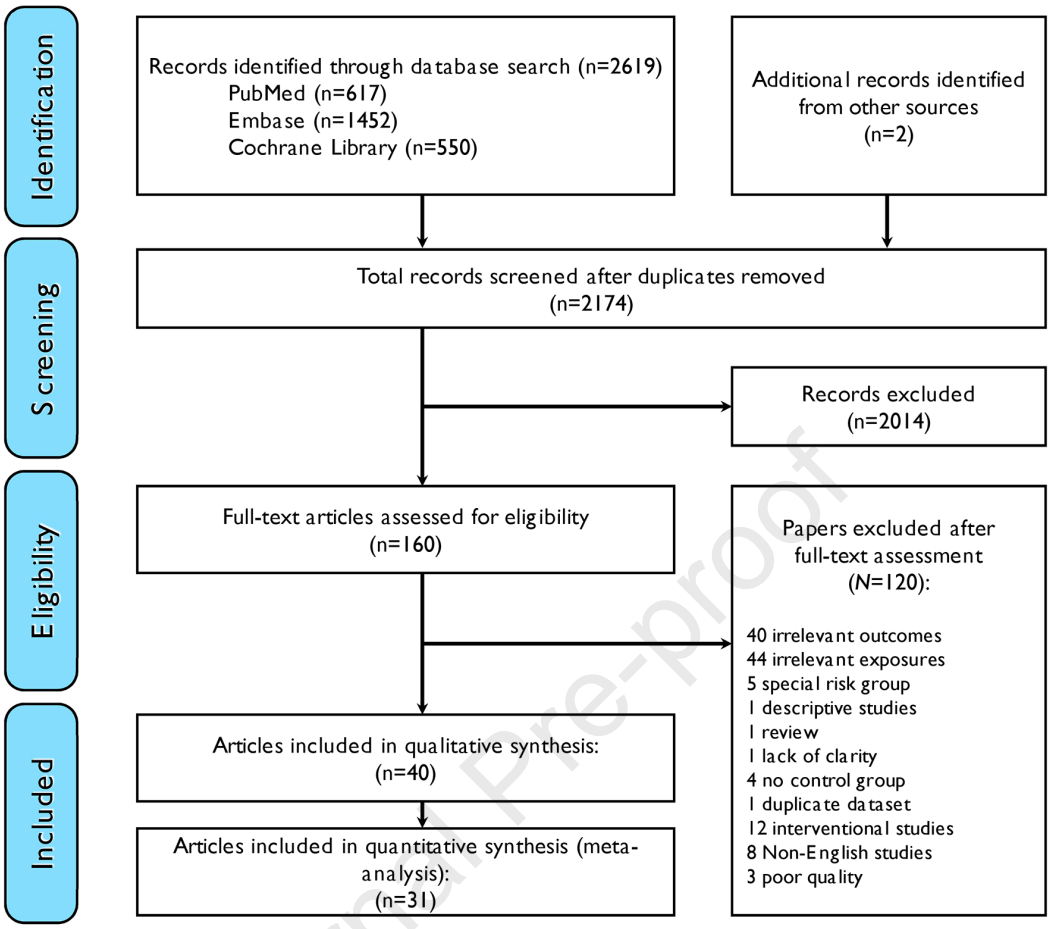

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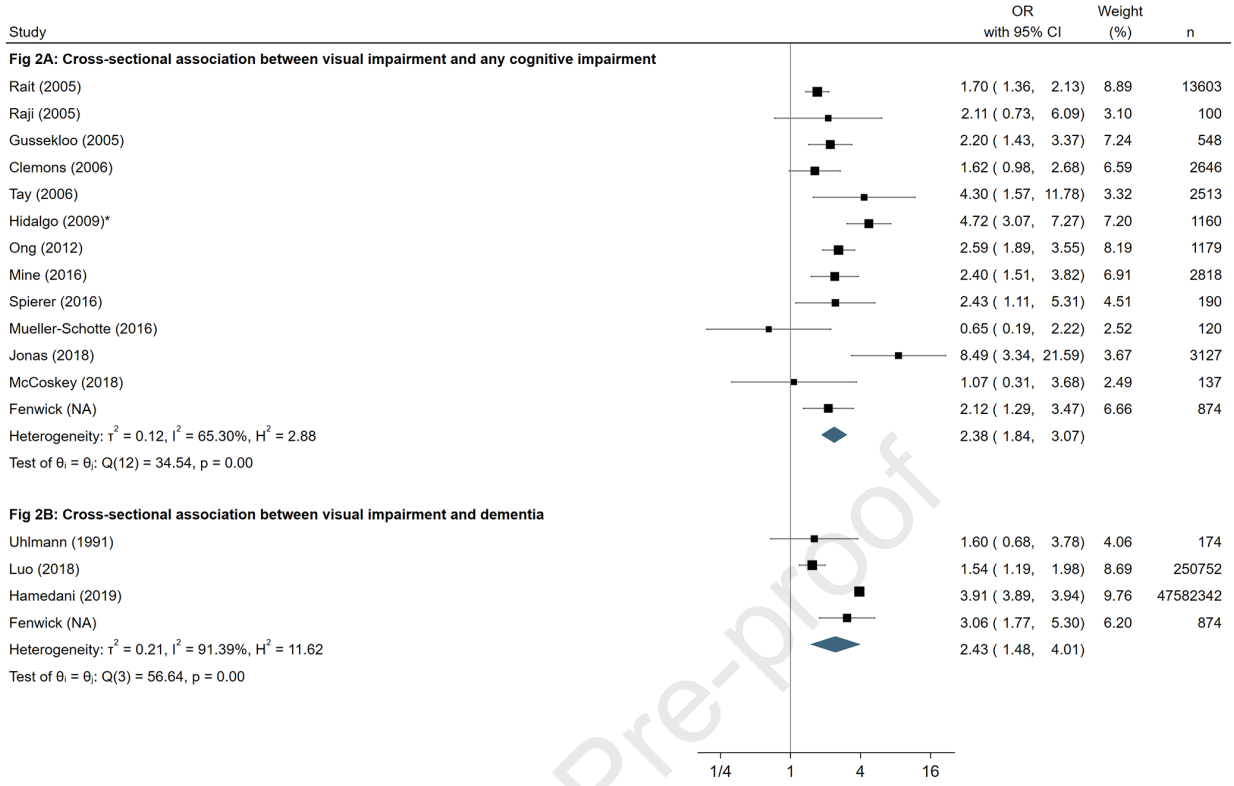

Box sizes reflect the study weights * Unadjusted study

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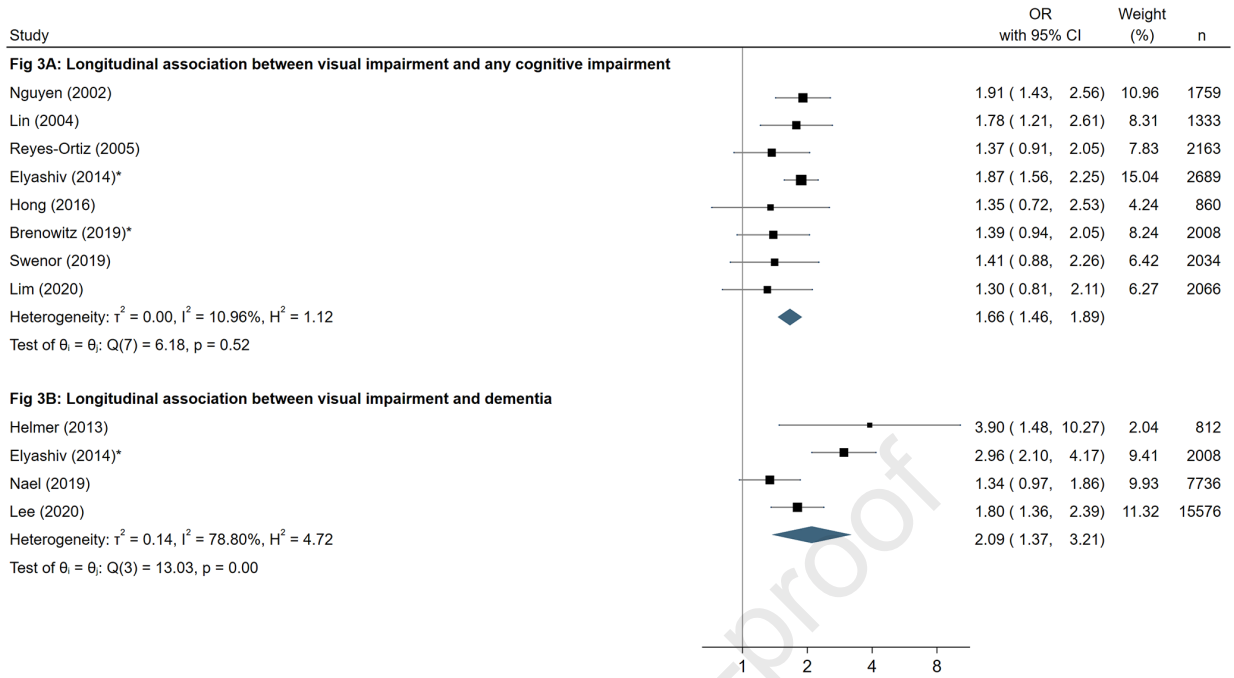

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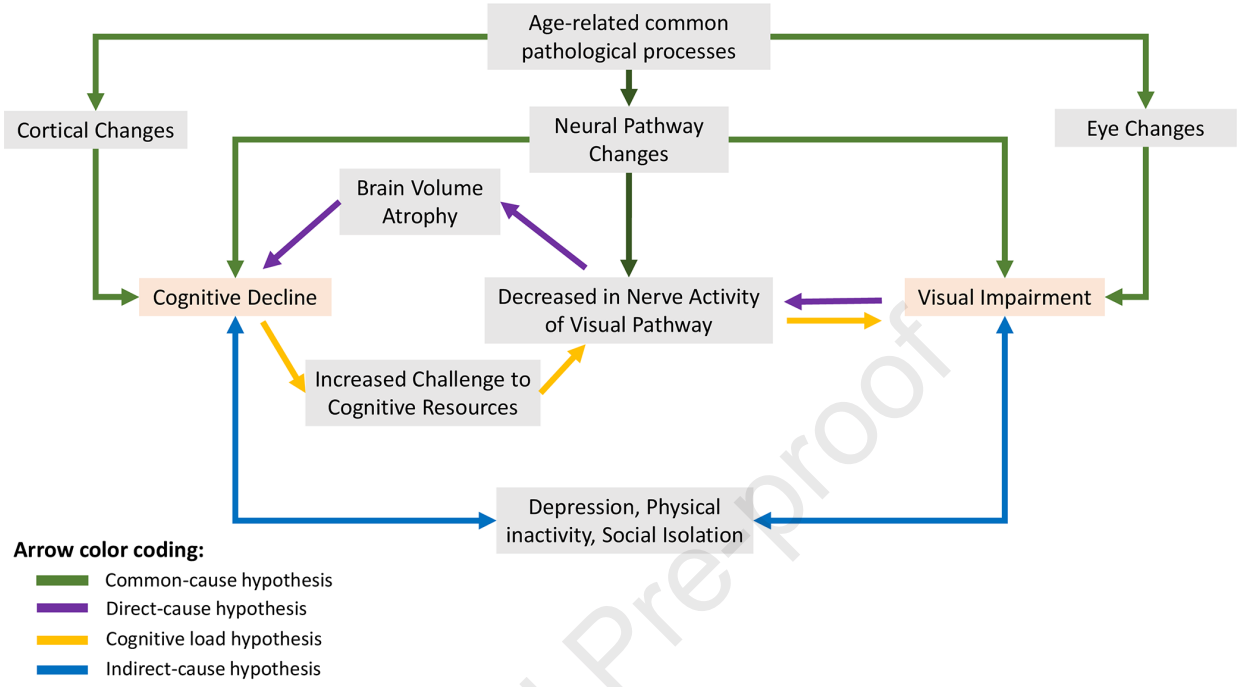

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PRÉCIS

Our systematic review and meta-analysis suggest a possible bidirectional relationship between visual and cognitive impairment. Strategies for early detection and management of these conditions in older people may minimize clinical and public health consequences.

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TITLE OF ARTICLE: THE BIDIRECTIONAL RELATIONSHIP BETWEEN VISION AND COGNITON: A SYSTEMATIC REVIEW AND META-ANALYSIS

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