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Visual Impairment, Eye Diseases, and Dementia Risk: A Systematic Review and Meta-Analysis

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Abstract.
Background: Visual impairment and eye diseases have been associated with dementia, though with mixed findings and often in cross-sectional studies.
Objective: To identify prospective studies investigating associations between visual impairment or common eye diseases and risk of all-cause dementia or key dementia subtypes.
Methods: We searched Medline, PsycINFO, and Embase from inception to January 2020. We also conducted backward and forward citation searches of included studies and set up alerts to identify studies published after the search date. Random-effects meta-analysis was used to combine adjusted estimates across studies.
Results: Thirty studies met our eligibility criteria. For visual impairment, pooled estimates indicated an increased risk of all-cause dementia (37,705 participants, 3,415 cases, risk ratio [RR] = 1.38, 95% confidence interval [CI]: 1.19–1.59, $I^2 = 28.6\%$). Pooled estimates also suggested an increased dementia risk associated with cataract (6,659 participants, 1,312 cases, hazard ratio [HR] = 1.17, 95% CI 1.00–1.38, $I^2 = 0.0\%$) and diabetic retinopathy (43,658 participants, 7,060 cases, HR = 1.34, 95% CI 1.11–1.61, $I^2 = 63.9\%$), respectively. There was no evidence of an association between glaucoma (175,357 participants, 44,144 cases, HR = 0.97, 95% CI 0.90–1.04, $I^2 = 51.5\%$) or age-related macular degeneration (7,800,692 participants, > 2,559 cases, HR = 1.15, 95% CI 0.88–1.50, $I^2 = 91.0\%$) and risk of dementia, respectively.
Conclusion: As visual impairment, cataract, and diabetic retinopathy are associated with an increased likelihood of developing dementia, early diagnosis may help identify those at risk of dementia. Given most causes of visual impairment are treatable or preventable, the potential for dementia prevention warrants further investigation.

Keywords: Alzheimer's disease, dementia, eye diseases, prospective studies, vision disorders

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INTRODUCTION

Identifying modifiable risk factors for dementia is of great importance given the lack of cure, with recent evidence recognizing sensory impairment including hearing and visual impairment (VI) as promising targets [1, 2]. Hearing loss has been highlighted as a key modifiable dementia risk factor by both Lancet Commissions [3, 4] on dementia prevention, intervention, and care. The evidence on VI is less well studied. VI is most frequently caused by uncorrected refractive errors and eye diseases (e.g., cataract, glaucoma), and typically defined by visual acuity [5]. VI is common at older ages, with 20–22% prevalence in those aged 70 and over [6]; however, in contrast to dementia, there are effective interventions for VI, with 80% of its causes being treatable (e.g., corrective lenses) or curable (e.g., cataract surgery) [5].

A recent meta-analysis of data from 14 and 12 prospective studies, respectively found visual impairment including color vision deficiency was associated with an increased risk of dementia (Risk Ratio [RR] = 1.47, 95% Confidence Interval [CI]: 1.36–1.60) and cognitive impairment (RR = 1.35, 95% CI: 1.28–1.41) [7]. A further meta-analysis of seven observational studies found glaucoma was associated with an increased risk of Alzheimer's disease (AD) (RR = 1.24, 95% CI: 1.02–1.51) [8]. However, restricting to five prospective studies resulted in no association between glaucoma and AD [8]. Similarly, a recent meta-analysis of one case-control and one cross-sectional study suggested an association between age-related macular degeneration (AMD) and cognitive impairment (Odds Ratio [OR] = 2.42, 95% CI: 1.06–5.56), whereas pooled results of two prospective studies indicated no association with AD (RR = 1.27, 95% CI: 0.53–3.04) [9]. Another systematic review found retinal microvascular changes were associated with dementia, cognitive dysfunction, and neuroimaging abnormalities, though most included studies were cross-sectional and no meta-analysis was conducted [10].

Recently, various prospective studies have been conducted which may help to clarify whether VI based on visual acuity is an independent dementia risk factor. Therefore, we conducted the first systematic review and meta-analysis of prospective studies investigating VI and common eye diseases, which cause VI, in relation to incident all-cause dementia or key dementia subtypes.

METHODS

Our systematic review was conducted according to the guidance provided by the Centre for Reviews and Dissemination (CRD, UK) [11]. Where possible, we performed random effects meta-analyses.

Search strategy, study selection, and data extraction

Following a pre-defined protocol (Supplementary Methods) and based on previous systematic reviews [6, 12, 13], we developed search strategies for Medline, PsycINFO, and Embase (via OvidSP) including subject headings and free text terms relevant to VI, common eye diseases, dementia, key dementia subtypes (AD, vascular dementia (VaD), dementia with Lewy bodies, frontotemporal dementia) and study design (Supplementary Figures 1–3). We conducted searches on 8 January 2020 (EK) supplemented by forward and backward citation searches of included publications and ongoing alerts to identify studies published after the search date. We included prospective studies in adults published in English investigating the association between VI or eye diseases and incident all-cause dementia or key dementia subtypes. The comparison group was no VI or in studies of eye disease, the eye disease of interest was not in the comparison group. We excluded studies with outcomes other than dementia or key dementia subtypes, studies using only a single cognitive measure or only self-reported dementia to define the outcome, studies investigating aspects of visual perception (e.g., color vision deficiency), studies with no comparison group or a comparison group other than no VI or no eye disease, and studies that were not prospective (e.g., case-control, cross-sectional, or retrospective studies). Animal studies, case reports, narrative reviews, letters, editorials, opinions, book chapters, conference abstracts, non-peer-reviewed publications, and duplicate publications using the same data were excluded. Two reviewers (EK, TJL) independently screened titles and abstracts, and reviewed full texts based on pre-defined inclusion and exclusion criteria discussing any discrepancies with a third reviewer (UT).

Study characteristics and fully adjusted results were extracted by one reviewer (EK) and checked by the second (TJL). Corresponding authors of 26 studies were contacted for clarification or additional data, with 11 providing a response (details in Supplementary Methods). Risk of bias of included studies

was assessed independently by the same two reviewers (EK, TJL) using the Quality Assessment Tool for Quantitative Studies [14] with discrepancies resolved by discussion. Overall risk of bias and potential sources of bias (selection bias, study design, confounders, blinding, data collection, withdrawals, and drop-outs [attrition bias]) were rated as strong, moderate, or weak according to the dictionary provided with the tool [14]. Detailed description of component ratings is provided in Supplementary Methods. In accordance with the tool, studies with no weak component ratings received a strong overall rating. Moderate and weak overall ratings were assigned to studies with only one and two or more weak component ratings, respectively.

Data analysis

Included studies were categorized based on exposure into those examining VI and eye diseases and outcome into all-cause dementia and key dementia subtypes. VI assessed with visual acuity was categorized into: no VI ($\leq$0.3 Logarithm of the Minimum Angle of Resolution [LogMAR]), mild VI (0.3 < LogMAR $\leq$ 0.5), moderate VI (0.5 < LogMAR $\leq$ 1.0), severe VI (1.0 < LogMAR $\leq$ 1.3), or blindness (1.3 < LogMAR) based on the World Health Organization (WHO) classification [5]. Studies where the comparison group was categorized as 'no VI' and the exposure as 'mild VI' or 'mild VI and worse' based on visual acuity assessment or self-report were added to a meta-analysis investigating the association between VI and dementia risk. We also conducted meta-analyses of the association between each eye disease and dementia risk. Given the heterogeneity between studies, we performed random effects meta-analyses using the *metan* command [15] in Stata 15.1 (StataCorp, College Station, TX, USA). Heterogeneity was investigated using Cochran's Chi-squared test and the I-squared statistic [16]. If multiple studies investigated the same exposure and outcome using overlapping data sources, we prioritized studies with a higher overall quality rating, bigger sample size, and published more recently. Pooled estimates are presented as hazard ratios (HRs) if studies included in meta-analysis reported only HRs. If included studies reported a mixture of HRs, RRs, and standardized rate ratios, we present pooled estimates as RRs [17]. Studies that could not be included in meta-analyses due to important methodological differences were synthesized narratively. In sensitivity analyses, we re-examined associations according to exposure ascertainment by repeating the VI and all-cause dementia meta-analysis after excluding studies with self-reported VI and pooling results for studies with low contrast sensitivity, open-angle glaucoma, and primary open-angle glaucoma as the exposures, respectively. We also repeated the main meta-analyses after excluding studies with a global risk of bias rating of weak if at least two studies with a global rating of moderate or strong remained.

RESULTS

Our searches resulted in 4,185 records. After removing 1,034 duplicates, 3,104 records were removed based on title and abstract screening resulting in 47 publications for full-text review, of which 21 met our inclusion criteria. Nine additional studies were identified via backward citation searches and alerts (Fig. 1) totaling in 30 included studies.

Key characteristics of included studies are provided in Table 1. Nine studies were from the United States, eight from Europe, and thirteen from Asia. Seventeen studies used electronic medical record datasets, eleven used data from population-based cohorts, and two performed *post-hoc* observational analyses of randomized controlled trial cohorts. Twenty-four studies used medical records ($n = 16$) or ophthalmic examination ($n = 8$) to identify VI or eye diseases, whereas six studies used self-report only ($n = 3$) or a combination of self-report and ophthalmic examination ($n = 2$), or a combination of self-report and medical records ($n = 1$). All-cause dementia or key dementia subtypes were ascertained based on medical records or a combination of sources (Supplementary Tables 2–7). Analytic sample sizes varied between the studies from 812 in a cohort study [18] to 7,766,857 in the biggest medical records study [19].

Risk of bias

Overall, three studies were rated as strong quality, 11 as moderate and 16 as weak (Supplementary Table 1). Studies with a moderate rating did not describe the validity and reliability of data collection method ($n = 7$) or were subject to potential attrition ($n = 3$) or selection bias ($n = 1$). Studies with a weak rating were subject to a combination of potential sources of bias including confounding ($n = 11$), validity and reliability of data collection method ($n = 10$), attrition ($n = 9$), selection bias ($n = 6$), and blinding ($n = 1$).

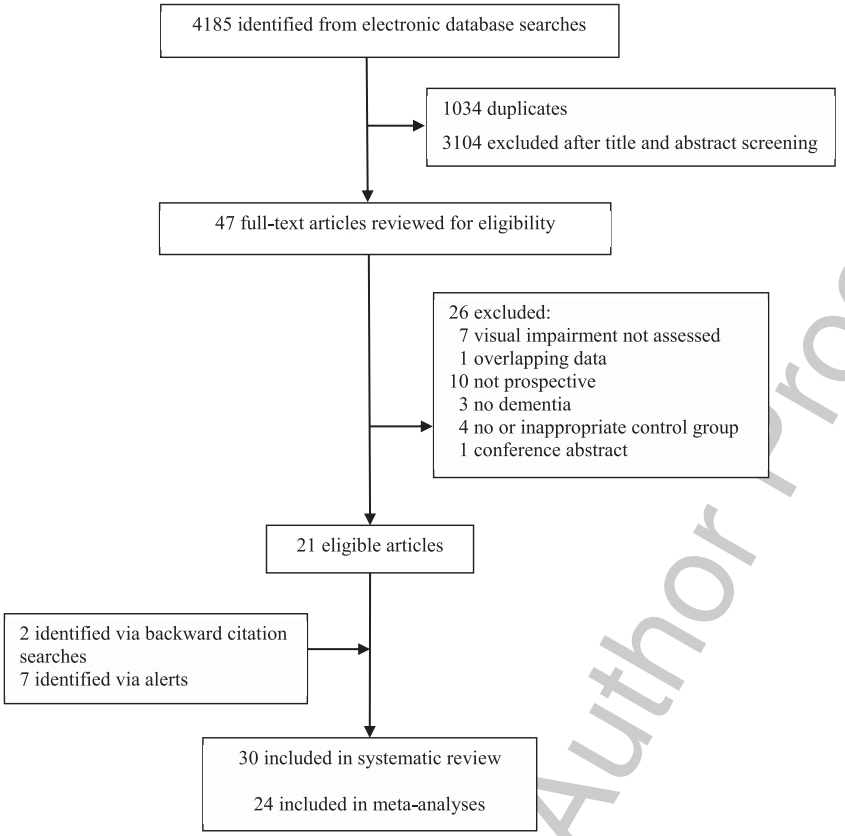

Fig. 1. Flowchart of search results and study retrieval.

Visual impairment and eye diseases

A narrative synthesis of additional findings on visual impairment, glaucoma, AMD, and diabetic retinopathy that could not be included in meta-analyses is provided in Supplementary Results.

Visual impairment

Ten cohort studies investigated the association between VI and incident all-cause dementia [20–29] (Supplementary Table 2). The pooled estimate of seven studies [20, 21, 23, 25–27, 29] indicated a higher risk of all-cause dementia in those with at least mild VI compared to no VI (37,705 participants, 3,415 dementia cases, pooled adjusted RR = 1.38, 95% CI: 1.19–1.59, $p < 0.001$, $I^2 = 28.6\%$; Fig. 2). After excluding three studies [21, 26, 29] using self-reported VI, the pooled estimate remained similar (26,381 participants, 2,651 dementia cases, pooled adjusted HR = 1.35, 95% CI: 1.10–1.67, $p = 0.005$, $I^2 = 38.7\%$; Supplementary Figure 4). The pooled estimate of two studies [20, 22] that assessed VI based on contrast sensitivity was also similar to our main finding although not statistically significant (3,892 participants, 565 dementia cases, pooled adjusted HR = 1.42, 95% CI: 0.82–2.48, $p = 0.21$, $I^2 = 79.7\%$; Supplementary Figure 5).

Three studies [28–30] investigated the association with incident AD (Supplementary Table 2). The pooled estimate of two studies [28, 29] indicated an increased risk of AD in those with at least mild VI compared to no VI (6,031,708 participants, 123,717 AD cases, pooled adjusted HR = 1.47, 95% CI: 1.43–1.50, $p < 0.001$, $I^2 = 0.0\%$; Supplementary Figure 6). Two studies [28, 29] investigated the association with VaD (Supplementary Table 2). Similarly, the pooled estimate of these two studies [28, 29] indicated an increased risk of VaD in those with at least mild VI compared to no VI (6,031,708 participants, 20,764 VaD cases, pooled adjusted HR = 1.40, 95% CI: 1.33–1.47, $p < 0.001$, $I^2 = 0.0\%$; Supplementary Figure 6).

Table 1
Key characteristics of included studies investigating the association between visual impairment, eye diseases and incident all-cause dementia or key dementia subtypes

Study	Country (data source)	Study design	Setting	Analytic sample size (dementia cases)	Mean baseline age (SD)	Women, %	Race/ethnicity*	Mean follow-up in years (SD)	Exposure	Outcome
Brenowitz et al. (2019) [20]	USA (Health ABC)	Cohort	Community	2,008 (378†)	77.4 (2.8)‡	51.8‡	34.8% Black, 65.2% White‡	6.5 (3.1)†	Visual acuity, contrast sensitivity	All-cause dementia
Chen et al. (2018) [31]	Taiwan (NHIRD)	Medical records cohort	Community	76,585 (3,597§)	62.1 (12.5)	45.3	>98% Asian¶	5.0 (3.3)	Normal and high tension glaucoma	All-cause dementia, AD
Choi et al. (2019) [42]	South Korea (KNHIS-HEALS)	Medical records cohort	Community	308,340 (7,457)	60.4 (7.8)	48.6	NR	up to 8	Age-related macular degeneration	AD
Davies-Kershaw et al. (2018) [21]	United Kingdom (ELSA)	Cohort	Community	8,648 (275)	66.9† (NR)	55.0	97.8% White, 2.2 % Non-white	11 (3.7†)	Self-reported vision	All-cause dementia
Ekström & Kilander (2014) [32]	Sweden (not given)	Cohort	Community	1,123 (174)	65–74#	56.1	100% White†	14.0 (6.4)	Open-angle glaucoma	All-cause dementia
Exalto et al. (2014) [45]	USA (KPNC Diabetes Registry)	Medical records cohort (type 2 diabetes)	Community	29,961 (5,173)	70.6 (6.8)	46.0	63.1% White, 11.4% African American, 11.0% Hispanic, 10.8% Asian, 2.8% Other	6.6 (NR)	Diabetic retinopathy	All-cause dementia
Fischer et al. (2016) [22]	USA (EHLS)	Cohort	Community	1,884 (187)	66.7 (8.4)	59.1	NR	up to 10	Contrast sensitivity	All-cause dementia
Helmer et al. (2013) [18]	France (3C Study)	Cohort	Community	812 (41)	79.7 (4.3)	64.7	NR	3**	Open-angle glaucoma	All-cause dementia
Hwang et al. (2020) [29]	USA (GEM Study)	Observational analysis of RCT cohort	Community	2,051 (321/220§/86††)	78.5 (3.1)	44.1	97.0% White, 3.0% Non-white	up to 8	Self-reported visual impairment	All-cause dementia, AD, VaD

(*Continued*)

Table 1
(Continued)

Study	Country (data source)	Study design	Setting	Analytic sample size (dementia cases)	Mean baseline age (SD)	Women, %	Race/ethnicity*	Mean follow-up in years (SD)	Exposure	Outcome
Keenan et al. (2015) [38]	United Kingdom (NHS HES)	Medical records cohort	Secondary care	2,623,130 (30,698§/ 29,520††)	55+	49.9	NR	up to 13	Primary open-angle glaucoma	AD, VaD
Keenan et al. (2014) [19]	United Kingdom (NHS HES)	Medical records cohort	Secondary care	7,766,857 (NR)	50+	61.5‡‡	NR	up to 12	Age-related macular degeneration	All-cause dementia, AD
Klaver et al. (1999) [30]	Netherlands (Rotterdam Study)	Cohort	Community	1,438 (62)	80.7 (4.5)	65.4	Largely White†	2.1 (NR)	Visual acuity, age-related macular degeneration	AD
Kuo et al. (2020) [33]	Taiwan (NHIRD)	Medical records cohort	Community	42,048 (2,304/ 183§/ 1,784††)	20–100#	50.0	>98% Asian¶	up to 16	Any glaucoma, open-angle glaucoma, normal tension glaucoma, angle-closure glaucoma	All-cause dementia, AD, VaD
Lai et al. (2014) [43]	Taiwan (NHIRD)	Medical records cohort	Community	39,908 (313)	71.6 (5.25)†	48.1	>98% Asian¶	7.91(3.32)†	Cataract	AD
Lee et al. (2019) [34]	USA (ACT)	Cohort	Community	3,877 (970†/ 792§)	74.3 (6.3)†	58	90% White	6.6 (4.5)†	Glaucoma, age-related macular degeneration, diabetic retinopathy, cataract	All-cause dementia, AD
Lee et al. (2020) [23]	China (EHC)	Medical records cohort	Community	15,576 (1,349)	74.5 (4.8)	63.8	100% Asian	5.0 (3.0–6.0)§§	Visual acuity	All-cause dementia

Lin et al. (2014) [39]	Taiwan (NHIRD)	Medical records cohort	Community	19,895 (208)	71.3 (7.3)	47.1	>98% Asian[¶]	1–8[#]	Primary open-angle glaucoma	AD
Maruta et al. (2020) [24]	Japan (LTCI)	Medical records cohort	Community	2,190 (1,153)	78.9 (6.1)	79.4	Not assessed[†]	8[†,**]	Visual acuity	All-cause dementia
Moon et al. (2018) [40]	South Korea (KNHIS)	Medical records cohort	Community	8,814 (742)	NR	47.1	100% Asian	7.0 (NR)[§§]	Primary open-angle glaucoma	AD
Naël et al. (2019) [25]	France (3C Study)	Cohort	Community	7,736 (882)	73.9 (5.4)	61.3	Not assessed[†]	9.1[§§] (4.0–11.3[†])	Near visual acuity, self-reported distance visual function	All-cause dementia
Nam et al. (2021) [47]	South Korea (KNHIS)	Medical records cohort	Community	185,036 (14,727/ 10,965[§]/ 1,788[††])	63.4 (10.1)	56.4	100% Asian[¶¶]	6.6 (1.4)	Retinal vein occlusion	All-cause dementia, AD, VaD
Ou et al. (2012) [35]	USA (Medicare)	Medical records cohort	Community	126,650 (40,528/ 21,531[§])	68+	65	86.9% White, 11% Black, 2.1% Other	up to 14	Open-angle glaucoma	All-cause dementia, AD
Paik et al. (2020) [28]	South Korea (KNHIS)	Medical records cohort	Community	6,029,657 (165,293/ 123,497[§]/ 20,678[††])	54.2 (10.5)	50.7	100% Asian[¶¶]	5.75 (0.92)	Visual acuity	All-cause dementia, AD, VaD
Rodill et al. (2018) [44]	USA (KPNC)	Medical records cohort (type 1 diabetes)	Community	3,742 (182)	56.1 (8.5)	47.4	79.0% White, 5.0% Black, 5.6% Hispanic, 3.9 % Asian, 3.9% Other/mixed, 2.6% Missing	6.2 (5.3)	Diabetic retinopathy	All-cause dementia
Rogers & Langa (2010) [26]	USA (HRS)	Cohort	Community	625 (168)	71+	61.3	7.9% Non-Caucasian	8.5 (2.4)	Self-reported vision	All-cause dementia
Schrijvers et al. (2012) [46]	Netherlands (Rotterdam Study)	Cohort	Community	6,078 (735/ 583[§]/80[††])	68.3 (8.4)	59	NR	11.4 (NR)	Diabetic retinopathy	All-cause dementia, AD, VaD

(*Continued*)

Table 1
(Continued)

Study	Country (data source)	Study design	Setting	Analytic sample size (dementia cases)	Mean baseline age (SD)	Women, %	Race/ethnicity*	Mean follow-up in years (SD)	Exposure	Outcome
Su et al. (2016) [36]	Taiwan (NHIRD)	Medical records cohort	Community	32,545 (1,601)	59.2 (17.2)	54.5	>98% Asian[¶]	6.3 (3.1)[†]	Glaucoma, primary angle-closure glaucoma, primary open-angle glaucoma	All-cause dementia
Tran et al. (2020) [27]	USA (WHI)	Observational analysis of RCT cohort	Community	1,061 (42)	73.8 (3.7)	100	90.4% White, 6.0% Black, 1.4% Hispanic, 0.3% American Indian, 0.8% Asian/Pacific Islander, 1.0% Other	3.8 (1.8)	Visual acuity, self-reported visual impairment	All-cause dementia
Tsai et al. (2015) [41]	Taiwan (NHIRD)	Medical records cohort	Community	29,958 (1,589)	74.5 (5.8)	47	>98% Asian[¶]	4.4 (2.5)	Age-related macular degeneration	All-cause dementia
Xiao et al. (2020) [37]	China (SAS)	Cohort	Community	1,659 (168/124[§])	71.5 (7.4)	54.2	NR	5.2 (NR)	Glaucoma, cataract	All-cause dementia, AD

ACT, Adult Changes in Thought; AD, Alzheimer's disease; AMD, age-related macular degeneration; DNHR, Danish National Hospital Register; DPCR, Danish Psychiatric Central Register; DR, diabetic retinopathy; EHC, Elderly Health Centres; EHLS, Epidemiology of Hearing Loss Study; Health ABC, Health, Aging, and Body Composition; GEM, Ginkgo Evaluation of Memory; HRS, Health and Retirement Study; KNHIS-HEALS, Korean National Health Insurance Service – Health Screening Cohort; KPNC, Kaiser Permanente Northern California; LTCI, Long-term Care Insurance; NA, not applicable; NHIRD, National Health Insurance Database; NHS HES, National Health Service Hospital Episode Statistics; NR, not reported; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma; RCT, randomized controlled trial; SAS, Shanghai Aging Study; VaD, vascular dementia; WHI, Women's Health Initiative; 3C, Three-City; *Percentages may not sum up to 100% due to rounding; [†]Additional information provided by the authors; [‡]Reported for the sample of 1,810; [§]AD; [¶]As described in Kuo et al. [33]; [#]Range; [**]All participants followed for the reported period; [††]VaD; [‡‡]Reported for the sample of 65,894 with age-related macular degeneration; [§§]Median (interquartile range); [¶¶]As described in Moon et al. [40].

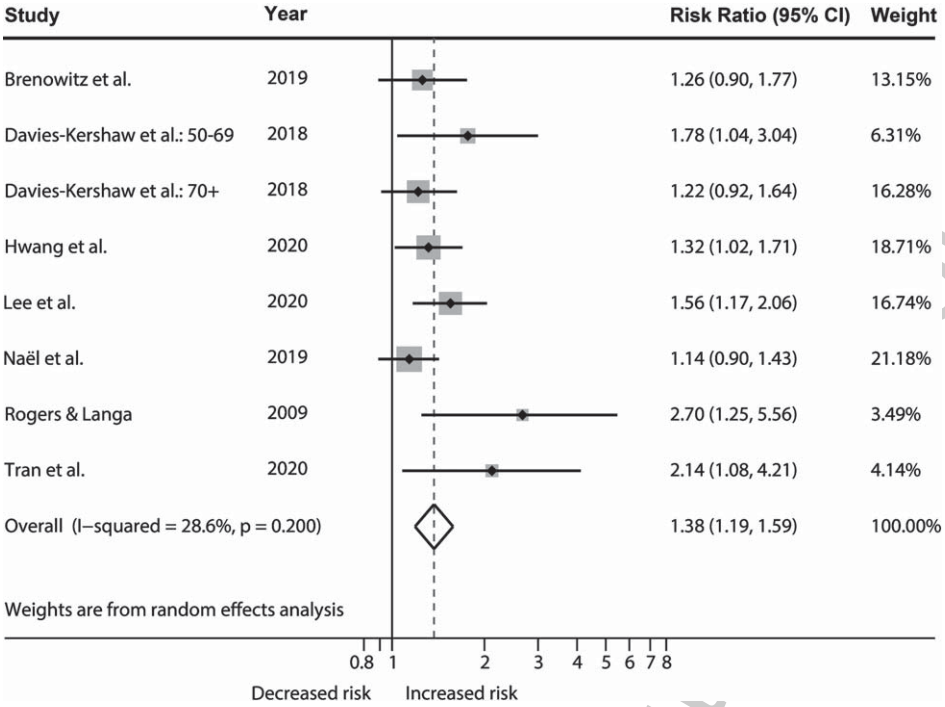

Fig. 2. Meta-analysis of risk ratios of at least mild visual impairment compared to no visual impairment on incident all-cause dementia. CI, confidence interval.

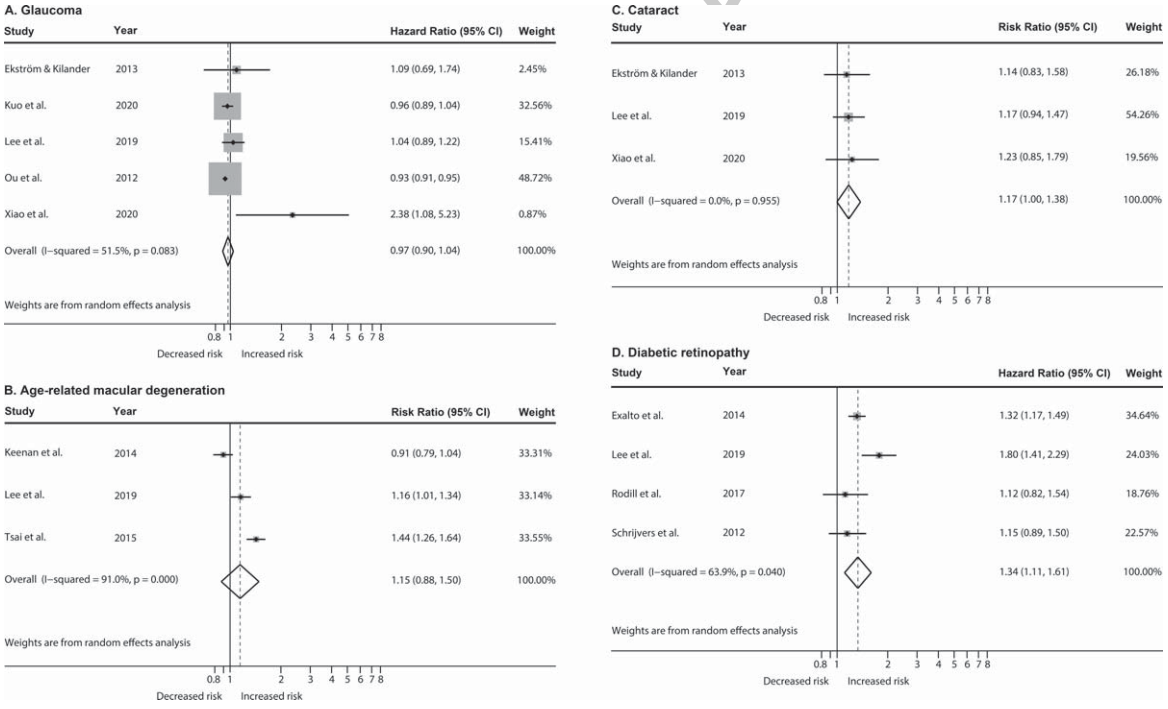

Fig. 3. Meta-analysis of risk ratios of eye disease compared to no given eye disease on incident all-cause dementia. CI, confidence interval.

Glaucoma

Eight cohort studies investigated the association between glaucoma and incident all-cause dementia [18, 31–37] (Supplementary Table 3). The pooled estimate of five studies [32–35, 37] suggested no association between glaucoma and all-cause dementia (175,357 participants, 44,144 dementia cases, pooled adjusted HR = 0.97, 95% CI: 0.90–1.04, $p = 0.38$, $I^2 = 51.5\%$; Fig. 3). In a sensitivity analysis restricting to studies on open-angle glaucoma only, the pooled estimate suggested a reduced risk of all-cause dementia associated with open-angle glaucoma (169,821 participants, 43,006 dementia cases, pooled adjusted HR = 0.93, 95% CI: 0.91–0.95, $p < 0.001$, $I^2 = 0.0\%$) (Supplementary Figure 7).

Eight cohort studies investigated the association between glaucoma and incident AD [31, 33–35, 37–40] (Supplementary Table 4). The pooled estimate of six studies [33–35, 37, 38, 40] suggested no association between glaucoma and AD (2,806,178 participants, 54,070 AD cases, pooled adjusted RR = 1.05, 95% CI: 0.93–1.17, $p = 0.45$, $I^2 = 87.5\%$; Fig. 4) compared to no glaucoma. When we restricted to primary open-angle glaucoma only, there was little evidence of an increased AD risk (2,651,839 participants, 31,648 AD cases, pooled adjusted RR = 1.23, 95% CI: 0.94–1.60, $p = 0.13$, $I^2 = 87.7\%$, Supplementary Figure 8).

Two cohort studies investigated the association between glaucoma and incident VaD [33, 38] (Supplementary Table 4). The pooled estimate suggested no association between open-angle glaucoma and VaD (2,665,178 participants, 31,304 VaD cases, pooled adjusted RR = 0.97, 95% CI: 0.73–1.27, $p = 0.81$, $I^2 = 90.7\%$; Supplementary Figure 7).

Age-related macular degeneration

Five cohort studies reported the association between AMD and incident all-cause dementia [19, 34, 41] ($n = 3$) and/or AD [19, 30, 34, 42] ($n = 4$; Supplementary Table 4). Pooled estimates of three studies [19, 34, 41] provided little evidence of an association between AMD and all-cause dementia (7,800,692 participants, > 2,559 dementia cases [exact number cannot be determined], pooled adjusted RR = 1.15, 95% CI: 0.88–1.50, $p = 0.30$, $I^2 = 91.0\%$, Fig. 3) or AD (8,079,074 participants, > 8,249 AD cases [exact number cannot be determined], pooled adjusted RR = 1.17, 95% CI: 0.88–1.54, $p = 0.28$, $I^2 = 85.2\%$, Fig. 4).

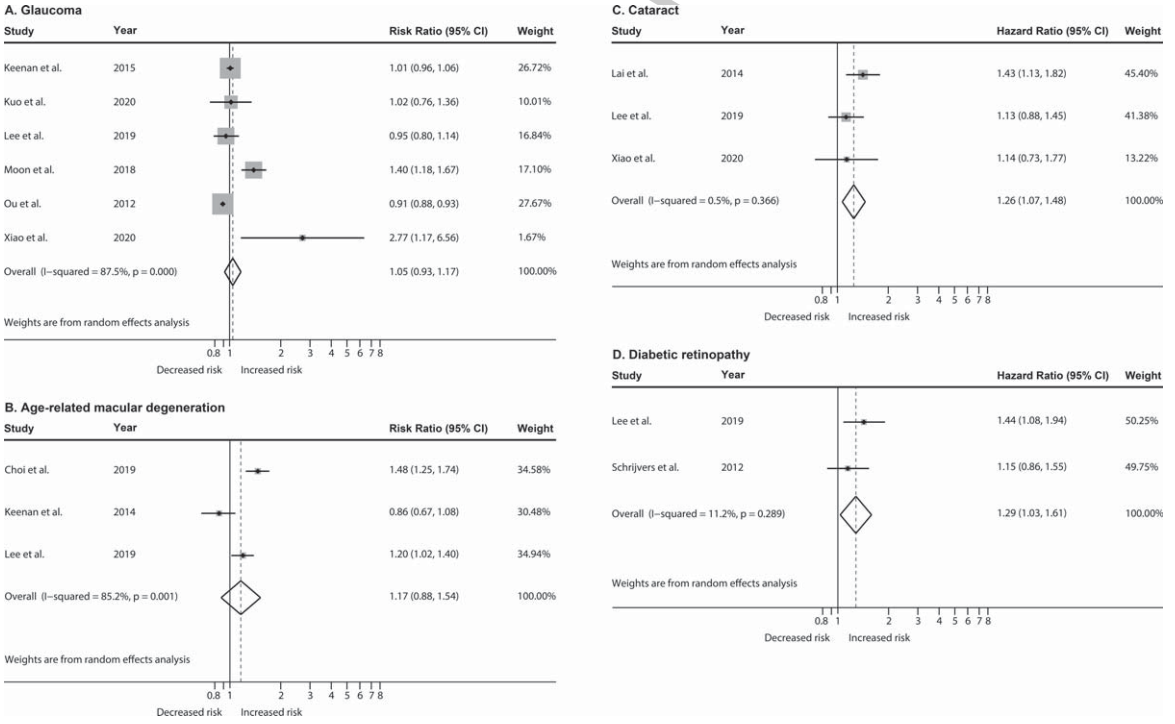

Fig. 4. Meta-analysis of risk ratios of eye disease compared to no given eye disease on incident Alzheimer's disease. CI, confidence interval.

Cataract

Four cohort studies investigated the association between cataracts and incident all-cause dementia [32, 34, 37] ($n = 3$) and/or AD [34, 37, 43] ($n = 3$; Supplementary Table 5). The pooled estimates suggested an increased risk of all-cause dementia (6,659 participants, 1,312 dementia cases, pooled adjusted RR = 1.17, 95% CI: 1.00–1.38, $p = 0.06$, $I^2 = 0.0\%$, Fig. 3) and of AD (45,444 participants, 1,229 AD cases, pooled HR = 1.26, 95% CI: 1.07–1.48, $p = 0.005$, $I^2 = 0.5\%$, Fig. 4) in those with cataract compared to no cataract.

Diabetic retinopathy

Four studies based on one type 1 diabetic cohort [44], one type 2 diabetic cohort [45] and two cohorts including non-diabetic participants [34, 46] investigated the association between diabetic retinopathy and incident all-cause dementia with one [46] and two [34, 46] studies, respectively, also investigating incident VaD and AD. The pooled estimate of four [34, 44–46] and two studies [34, 46], respectively, indicated an increased risk of all-cause dementia (43,658 participants, 7,060 dementia cases, pooled adjusted HR = 1.34, 95% CI: 1.11–1.61, $p = 0.002$, $I^2 = 63.9\%$, Fig. 3) and AD (9,955 participants, 1,375 AD cases, pooled adjusted HR = 1.29, 95% CI: 1.03–1.61, $p = 0.03$, $I^2 = 11.2\%$, Fig. 4) in those with diabetic retinopathy compared to no retinopathy. Only one study [46] (6,078 participants, 80 VaD cases) investigated diabetic retinopathy and VaD; this provided little evidence of an association (HR = 0.90, 95% CI: 0.39–2.11).

Other eye diseases

One study [47] investigating the association with retinal vein occlusion using medical records suggested an increased risk of incident all-cause dementia (185,036 participants, 14,727 dementia cases, HR = 1.16, 95% CI: 1.12–1.21), AD (185,036 participants, 10,965 AD cases, HR = 1.15, 95% CI: 1.11–1.20), and VaD (185,036 participants, 1,788 VaD cases, HR = 1.24, 95% CI: 1.12–1.37) compared to no retinal vein occlusion (Supplementary Table 7).

Additional analyses

Associations remained similar when we repeated analyses with only studies that received a global risk of bias rating of moderate or strong. Pooled estimates for these analyses are provided in Supplementary Results.

DISCUSSION

Results of our systematic review and meta-analyses indicate that VI based on visual acuity was associated with incident all-cause dementia, AD, and VaD. The association with all-cause dementia was robust to exclusion of studies using self-reported VI and studies with a weak global risk of bias rating. However, there was no association between VI measured using contrast sensitivity and dementia. Diabetic retinopathy was also associated with an increased dementia and AD risk. There was weaker evidence for an increased dementia and AD risk in those with cataract. We found no evidence of an association between glaucoma or AMD and risk of dementia or key dementia subtypes.

Our findings are in line with results of a recently published meta-analysis reporting similar pooled estimates of the association between visual impairment and incident dementia or cognitive impairment [7]. However, we applied more stringent inclusion and exclusion criteria (e.g., exclusion of studies investigating color vision deficiency, studies including overlapping data and non-peer-reviewed publications) potentially resulting in more conservative estimates. Nevertheless, despite the different criteria for study selection, the findings from both meta-analyses provide consistent evidence that VI is associated with a 38%–47% increased risk of dementia.

In our meta-analysis, the exposure was defined as at least mild VI, so when comparing to no VI the strength of the relationship between moderate or severe VI and dementia might have been underestimated. For example, Paik and colleagues [28] reported stronger associations for moderate VI (HR = 1.74, 95% CI: 1.70–1.78) and severe VI/blindness (HR = 1.75, 95% CI: 1.71–1.79) than for mild VI (HR = 1.45, 95% CI: 1.42–1.48) compared to normal vision. Some studies included in the systematic review also found higher dementia risk in those with more severe VI, but only contributed results for 'mild' VI to the pooled estimates [21, 23, 25].

The association between VI and dementia risk could be mediated by other dementia risk factors, e.g., social isolation, depressive symptom, and physical inactivity [3]. Findings from the Three-City study [25] and the Canadian Longitudinal Study on Aging

[48] suggest that engagement in cognitively stimulating activities and social engagement only weakly mediate this association. However, the prevalence of depression is higher in those with VI compared to normal vision [49] and dementia risk increased only in those with depressive symptoms in the Three-City study [25]. Physical inactivity is an established dementia risk factor [3] also related to VI where VI may lead to decreased physical activity whereas being physically active may protect against VI [50]. Nevertheless, the relationships are complex as the proposed mediators may increase dementia risk, be an early sign of dementia [3], or be bi-directionally related with VI [50, 51].

VI often co-occurs with hearing impairment, another form of sensory deprivation which has recently been highlighted as a potential modifiable risk factor for dementia [3]. Both sensory impairments may share common pathways [52] and the risk of dementia might be greater in the presence of both VI and hearing impairment. Two [27, 29] of the studies included in the systematic review investigated both impairments. Hwang and colleagues [29] found dual sensory impairment was associated with a much higher dementia risk (HR = 1.86, 95% CI:1.25–2.76) than single impairment (HR = 1.11, 95% CI:0.86–1.44) compared to no sensory impairment. In analyses stratified by self-reported hearing loss, Tran and colleagues [27] reported a stronger association between VI and dementia risk in those with hearing loss. However, only two additional studies [23, 25] investigating VI adjusted their analyses for hearing impairment. Further studies clarifying whether VI and hearing impairment independently or interactively increase the risk of dementia are therefore warranted

Glaucoma and AD are both neurodegenerative diseases and share pathogenic mechanisms, such as axonal degeneration, altered levels of Aβ and tau proteins, cerebrospinal fluid circulatory failure, and autophagy [53]. Therefore, glaucoma could either increase the risk of dementia due to VI or commonly co-occur due to these shared mechanisms. However, our findings are similar to a previous meta-analysis of five prospective studies [8] which suggested no association between glaucoma and AD.

Shared risk factors (e.g., smoking, hypertension, obesity) and cellular processes (e.g., oxidative stress, chronic inflammation, ubiquitination) have been also suggested for AMD and AD [54]. However, neither results of our meta-analysis nor findings of a previous meta-analysis when restricted to prospective studies [9] provide evidence for an association between AMD and dementia risk. Common risk factors (e.g., age, smoking, low socioeconomic status) may also explain an increased risk of all-cause dementia and AD in those with cataract in our meta-analyses [55].

Diabetes, often accompanied by damage to the retina, is an established risk factor for all-cause dementia (RR = 1.43, 95% CI: 1.33–1.53), AD (RR = 1.43, 95% CI: 1.25–1.62) and VaD (RR = 1.91, 95% CI: 1.61–2.25) [56]. Our meta-analyses yielded similar estimates for the association of diabetic retinopathy with all-cause dementia or AD. Therefore, common metabolic and vascular pathways (e.g., hyperglycemia, hyperlipidemia, hypertension) underling both dementia and diabetic retinopathy are possible. Retinal microvascular changes may indicate cerebral vascular disease given that retinal vessels are similar to cerebral microvasculature and have been suggested as potential dementia biomarkers [10, 57].

Included studies differed considerably in exposure ascertainment. Most studies of VI used visual acuity tests or relied on self-report whereas most studies of eye diseases were based on medical records. Eye diseases captured through medical records would be expected to be treated and therefore could have biased the results towards the null. Indeed, a systematic review and meta-analysis of cataract surgery indicated an improvement in cognitive function and reduction of depressive symptoms after cataract treatment [58]. Moreover, some cases of eye diseases and dementia may not be recorded in medical records, also biasing the results towards the null. Furthermore, in studies focusing on specific eye diseases, the comparison group will include individuals with other eye diseases (unless explicitly excluded). Again, this could bias the results towards the null, if the hypothesis is that VI increases the risk of dementia, rather than specific conditions. The length of follow-up of studies included in our systematic review ranged up to 16 years [33] but changes in the brain may occur even 20 years before the onset of dementia symptoms [59]. Moreover, not all included studies were specifically designed to investigate the association between VI and dementia, and generally there was high degree of heterogeneity between the studies reflecting methodological differences, e.g., in sample selection, adjustment strategy, exposure, and outcome ascertainment. Half of the studies included in meta-analyses received a risk of bias rating of weak. Therefore, further well-designed studies are

needed to investigate the association between VI, eye diseases, and risk of dementia and key dementia subtypes. Our search strategy was limited to three databases and focused on VI in general and common eye diseases, not including contrast sensitivity specifically or rarer eye diseases. Therefore, we cannot exclude the possibility that not all relevant studies were captured. Finally, the observational nature of the studies included in the review limit any causal inferences on the associations observed.

In conclusion, this systematic review and meta-analysis of VI and its major causes provides evidence for the association between VI and increased dementia risk. Diabetic retinopathy and cataract but not glaucoma and AMD were also associated with increased dementia risk. Diagnosing VI may help identify those at risk of developing dementia. Given that VI is highly prevalent and most causes of VI are treatable, the potential for dementia prevention of early interventions to reduce VI warrants further investigation.

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SUPPLEMENTARY MATERIAL

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