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: Dementia, Alzheimer disease, eye diseases, vision disorders, prospective studies

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 ≤ 0.5), moderate VI ($0.5 < $ LogMAR ≤ 1.0), severe VI ($1.0 < $ LogMAR ≤ 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 (Figure 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).

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

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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%; Figure 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).

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%;

Figure 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%; Figure 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%, Figure 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%, Figure 4).

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%, Figure 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%, Figure 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%, Figure 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%, Figure 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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Conflict of interest / disclosure statement

E. Kuźma, T J. Littlejohns, D.J. Lewellyn and O.C. Ukoumunne have no conflict of interest to report.

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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	Medical records cohort	Community	308,340 (7,457)	60.4 (7.8)	48.6	NR	up to 8	Age-related macular degeneration	AD

	(KNHIS-HEALS)									
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%	6.6 (NR)	Diabetic retinopathy	All-cause dementia

							Hispanic, 10.8% Asian, 2.8% Other			
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
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%	up to 14	Open-angle glaucoma	All-cause dementia, AD

							Black, 2.1% Other			
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	USA (HRS)	Cohort	Community	625 (168)	71+	61.3	7.9% Non-Caucasian	8.5 (2.4)	Self-reported vision	All-cause dementia

(2010) [26]										
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
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%	3.8 (1.8)	Visual acuity, self-reported visual impairment	All-cause dementia

							American Indian, 0.8% Asian/Pacific Islander, 1.0% Other			
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]

Figure 1. Flowchart of search results and study retrieval

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┌─────────────────────────────────────────────────┐
│ 4185 identified from electronic database searches │
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                    │
                    │        ┌────────────────────────────────────────────┐
                    ├───────▶│ 1034 duplicates                             │
                    │        │ 3104 excluded after title and abstract      │
                    │        │ screening                                   │
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┌─────────────────────────────────────────────────┐
│ 47 full-text articles reviewed for eligibility   │
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                    │        │ 26 excluded:                                │
                    │        │   7 visual impairment not assessed          │
                    │        │   1 overlapping data                        │
                    ├───────▶│ 10 not prospective                          │
                    │        │   3 no dementia                             │
                    │        │   4 no or inappropriate control group       │
                    │        │   1 conference abstract                     │
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                    ▼
            ┌─────────────────────┐
            │ 21 eligible articles │
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│ 2 identified via backward citation │
│ searches                          │───────▶
│ 7 identified via alerts           │
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            ┌──────────────────────────────────┐
            │ 30 included in systematic review  │
            │ 24 included in meta-analyses      │
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Study	Year	Risk Ratio (95% CI)	Weight
Brenowitz et al.	2019	1.26 (0.90, 1.77)	13.15%
Davies-Kershaw et al.: 50-69	2018	1.78 (1.04, 3.04)	6.31%
Davies-Kershaw et al.: 70+	2018	1.22 (0.92, 1.64)	16.28%
Hwang et al.	2020	1.32 (1.02, 1.71)	18.71%
Lee et al.	2020	1.56 (1.17, 2.06)	16.74%
Naël et al.	2019	1.14 (0.90, 1.43)	21.18%
Rogers & Langa	2009	2.70 (1.25, 5.56)	3.49%
Tran et al.	2020	2.14 (1.08, 4.21)	4.14%
Overall (I−squared = 28.6%, p = 0.200)		1.38 (1.19, 1.59)	100.00%

Weights are from random effects analysis

0.8 1 2 3 4 5 6 7 8
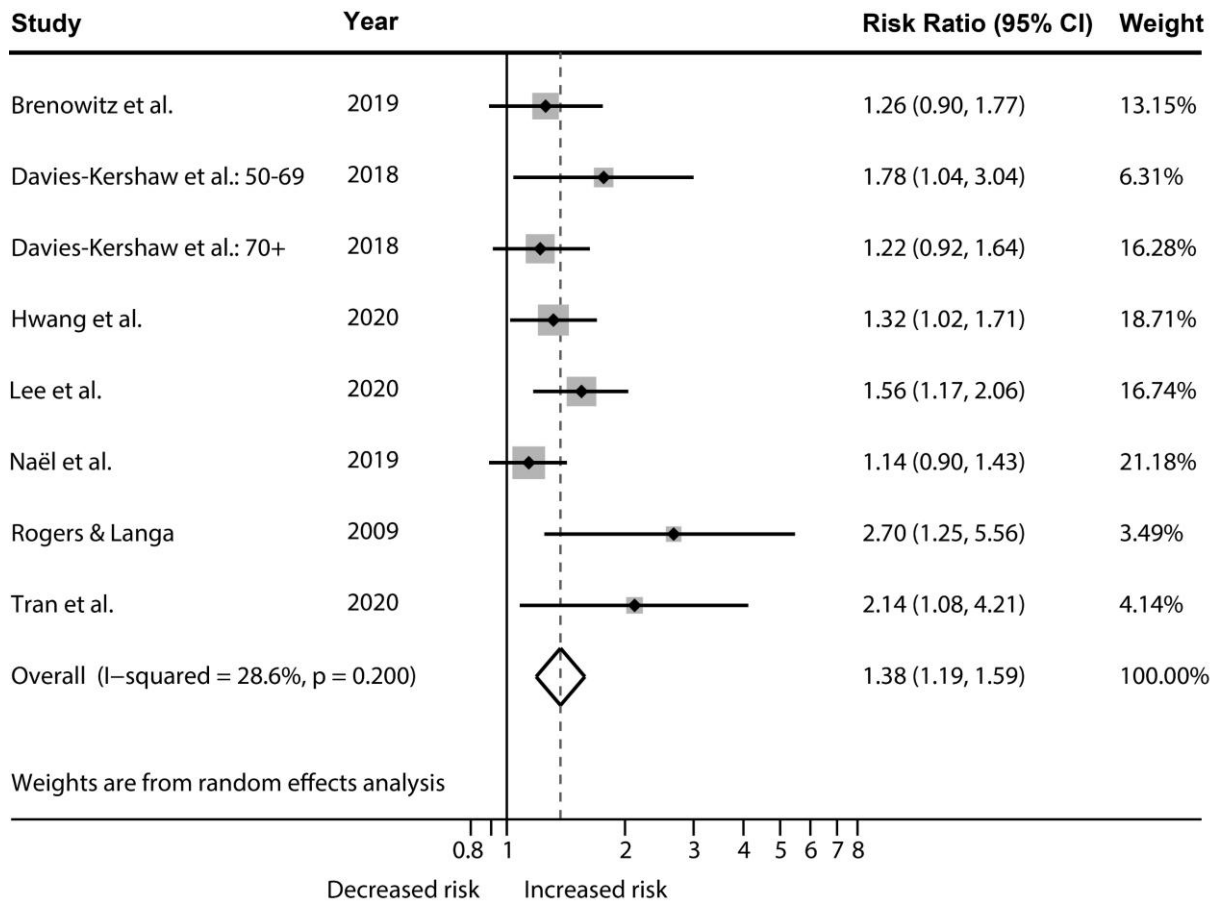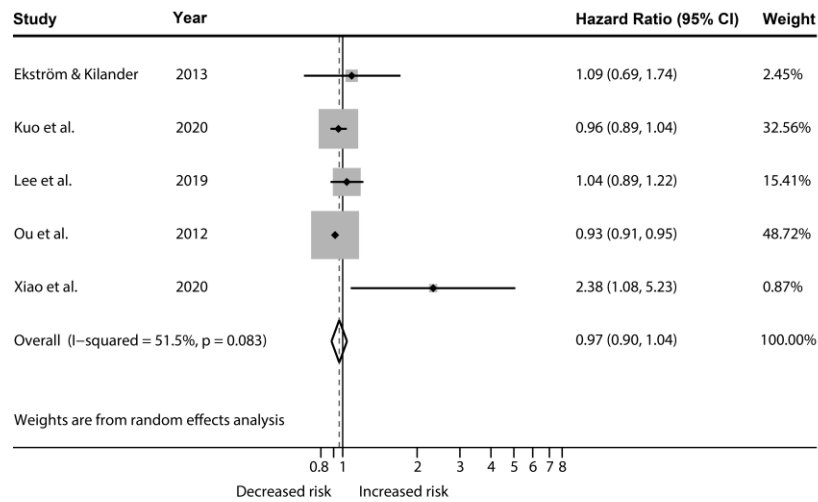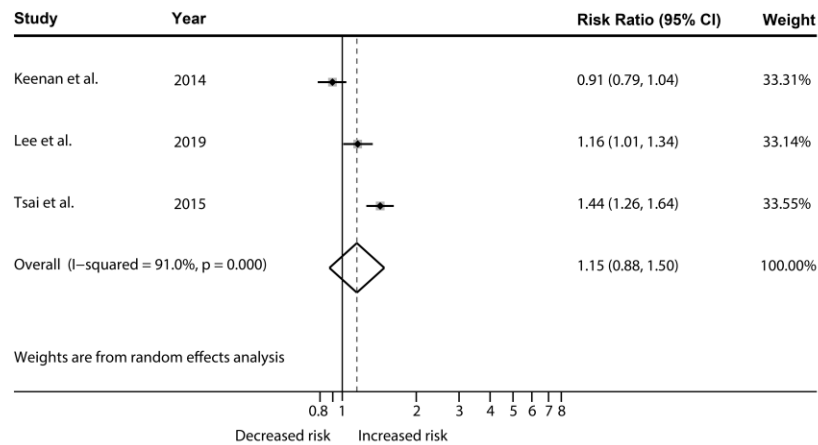
Decreased risk   Increased risk

Figure 2. Meta-analysis of risk ratios of at least mild visual impairment compared to no visual impairment on incident all-cause dementia

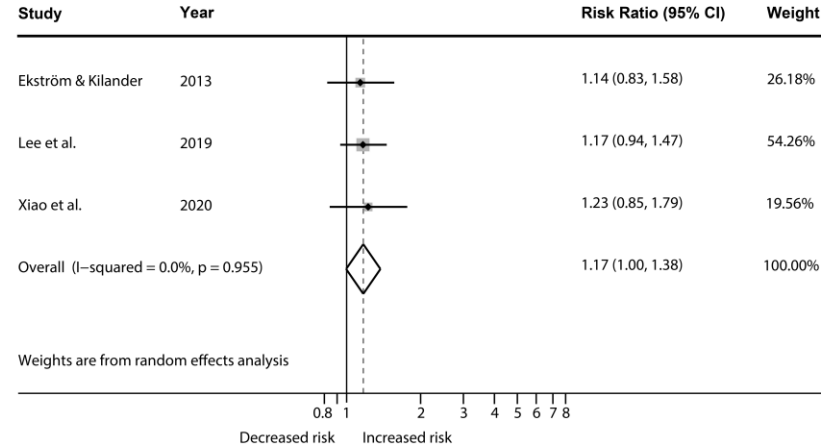Abbreviations: CI, confidence interval

A. Glaucoma

Study	Year		Hazard Ratio (95% CI)	Weight
Ekström & Kilander	2013		1.09 (0.69, 1.74)	2.45%
Kuo et al.	2020		0.96 (0.89, 1.04)	32.56%
Lee et al.	2019		1.04 (0.89, 1.22)	15.41%
Ou et al.	2012		0.93 (0.91, 0.95)	48.72%
Xiao et al.	2020		2.38 (1.08, 5.23)	0.87%
Overall (I−squared = 51.5%, p = 0.083)			0.97 (0.90, 1.04)	100.00%

Weights are from random effects analysis

0.8 1   2   3   4 5 6 7 8
Decreased risk   Increased risk

B. Age-related macular degeneration

Study	Year		Risk Ratio (95% CI)	Weight
Keenan et al.	2014		0.91 (0.79, 1.04)	33.31%
Lee et al.	2019		1.16 (1.01, 1.34)	33.14%
Tsai et al.	2015		1.44 (1.26, 1.64)	33.55%
Overall (I−squared = 91.0%, p = 0.000)			1.15 (0.88, 1.50)	100.00%

Weights are from random effects analysis

0.8 1   2   3   4 5 6 7 8
Decreased risk   Increased risk

C. Cataract

Study	Year		Risk Ratio (95% CI)	Weight
Ekström & Kilander	2013		1.14 (0.83, 1.58)	26.18%
Lee et al.	2019		1.17 (0.94, 1.47)	54.26%
Xiao et al.	2020		1.23 (0.85, 1.79)	19.56%
Overall (I−squared = 0.0%, p = 0.955)			1.17 (1.00, 1.38)	100.00%

Weights are from random effects analysis

0.8 1   2   3   4 5 6 7 8
Decreased risk   Increased risk

D. Diabetic retinopathy

Study	Year		Hazard Ratio (95% CI)	Weight
Exalto et al.	2014		1.32 (1.17, 1.49)	34.64%
Lee et al.	2019		1.80 (1.41, 2.29)	24.03%
Rodill et al.	2017		1.12 (0.82, 1.54)	18.76%
Schrijvers et al.	2012		1.15 (0.89, 1.50)	22.57%
Overall (I−squared = 63.9%, p = 0.040)			1.34 (1.11, 1.61)	100.00%

Weights are from random effects analysis

0.8 1   2   3   4 5 6 7 8
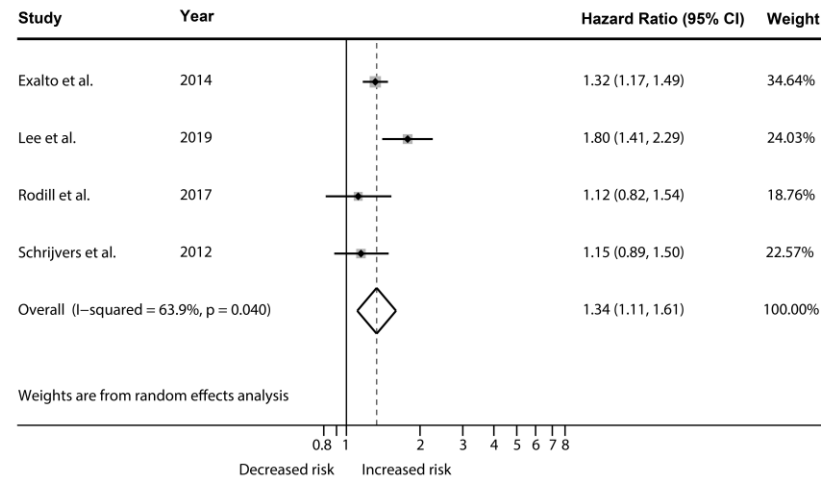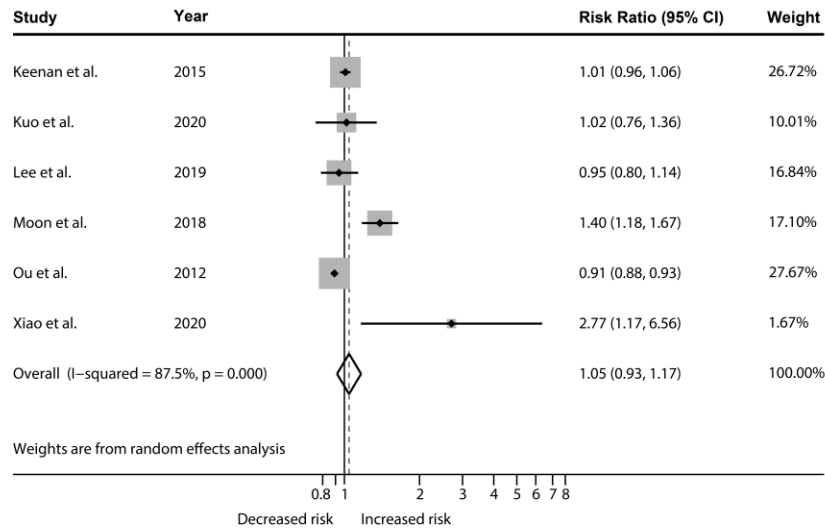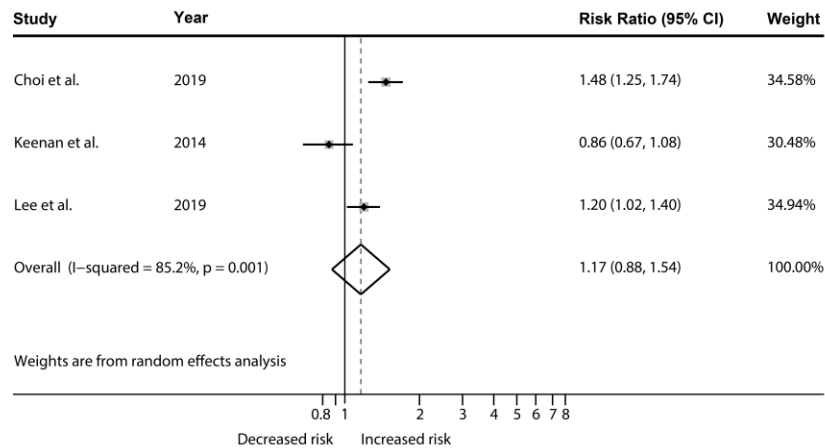Decreased risk   Increased risk

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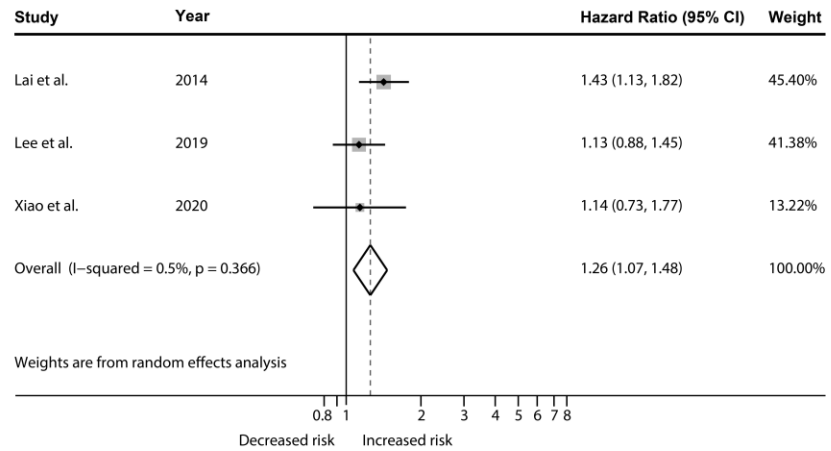
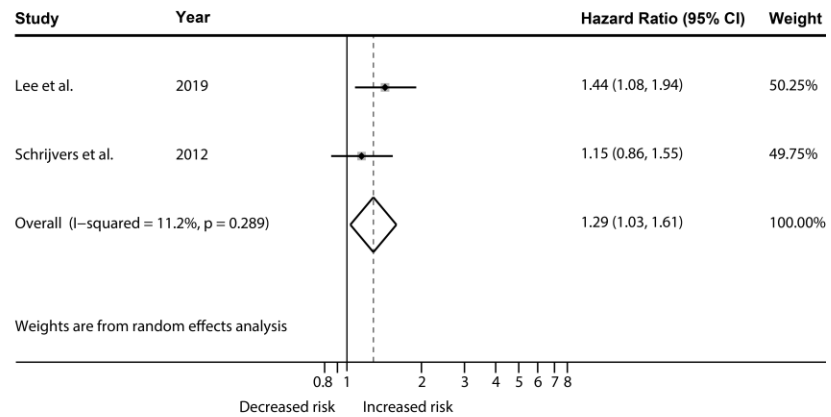Abbreviations: CI, confidence interval

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Figure 4. Meta-analysis of risk ratios of eye disease compared to no given eye disease on incident Alzheimer's disease

Abbreviations: CI, confidence interval

Supplementary Methods

<u>Review Protocol</u>

Review question: Do prospective studies suggest an increased risk of all-cause dementia or key dementia subtypes (Alzheimer's disease, vascular dementia, dementia with Lewy bodies, frontotemporal dementia) associated with visual impairment and eye diseases?

Population: Adults (≥18 years)

Exposure: Visual impairment and eye conditions (e.g. glaucoma, age-related macular degeneration, cataract and retinopathy)

Comparators: No visual impairment (i.e. normal vision) or no eye condition

Outcomes: Incident all-cause dementia or key dementia subtypes

Search strategy:

- Searching the following databases: Medline, Embase, PsycINFO (via OvidSP)
- Backward and forward citation searching of included studies via Web of Science
- Alerts to identify studies published after the search date

Study selection criteria:

Inclusion criteria:

- Prospective studies on the association between visual impairment or eye diseases and incident all-cause dementia or key dementia subtypes
- Only publications in English

Exclusion criteria:

- Studies with outcomes that are not directly dementia-related (e.g. neuroimaging or biomarkers)
- Studies with no comparison group or comparison group other than no visual impairment or no eye disease
- Studies using only a single cognitive instrument or self-reported dementia to define incident all-cause dementia or key dementia subtypes
- studies investigating aspects of visual perception (e.g. color vision deficiency)
- Animal studies
- Case reports, narrative reviews, letters, editorials, opinions, book chapters
- Conference abstracts
- Duplicate publications using the same data

Study selection: Two reviewers (EK & TJL) will independently screen titles and abstracts based on the inclusion/exclusion criteria. The same two reviewers will also review

independently full-texts of potentially relevant studies. Any discrepancies will be resolved by discussion, if necessary with a third reviewer (UT).

Risk of bias assessment: Two reviewers (EK & TJL) will independently assess the risk of bias using the Quality Assessment Tool for Quantitative Studies [1]. Seven components will be rated individually as strong, moderate or weak in the following way:

1. **Selection bias** will be rated as strong if study participants are likely to be representative of the target population and the participation rate at baseline is greater than 80%, as moderate if participants are at least somewhat likely to be representative of the target population and the participation rate at baseline is 60-79%, and as weak if participants are not likely to be representative of the target population or the participation rate at baseline is less than 60% or selection and participation rate at baseline are not described,

2. **Design** will be rated as strong for randomized controlled trials and controlled clinical trials, as moderate for cohort studies, case control studies or interrupted time series and as weak for any other method or if method is not described.

3. **Confounders**. We consider adjusting analyses for sociodemographic confounders (age, sex, education and / or socioeconomic status, and ethnicity in case of a heterogenous sample) as essential. Studies will be rated as strong if analyses are adjusted for sociodemographic and at least three additional confounders and as moderate if adjustment strategy includes sociodemographic and one or two additional confounders. Studies will receive a weak rating if only sociodemographic or not all relevant sociodemographic confounders are adjusted for.

4. **Blinding** will be rated as strong if the outcome assessor is not aware of participants' visual status and participants are not aware of the research question / assessment of visual function for research purposes, as moderate if the outcome assessor is not aware of participants' visual status or participants are not aware of the research question / assessment of visual function for research purposes or blinding is not described and as weak if the outcome assessor is aware of participants' visual status and participants are aware of the research question / assessment of visual function for research purposes.

5. **Data collection methods** will be rated as strong if data collection tools have been shown or are widely known to be valid and reliable, as moderate if data collection tools have been shown or are widely known to be valid but not reliable or reliability is not described and as weak if data collection tools have been shown or are widely known not to be valid or both validity and reliability are not described.

6. **Withdrawals and drop-outs (attrition bias)** will be rated as strong if the follow-up rate is at least 80%, as moderate if the follow-up rate is 60-79% or follow-up rate cannot be assessed due to study design (not applicable) and as weak if the follow-up rate is less than 60% or withdrawals and drop-outs are not described.

Any discrepancies will be resolved by discussion, if necessary with a third reviewer (UT). We will include funnel plots to investigate publication bias if there are at least ten studies included in a meta-analysis [2].

Data extraction: One reviewer (EK) will extract key data including study design, assessment of exposures and outcomes, population, adjusted estimates of the association between exposure and outcome, adjustment strategy and sources of data. Data extraction will be checked by the second reviewer (TJL). Any discrepancies will be resolved by discussion, if necessary with a third reviewer (UT).

Evidence synthesis methods: The identified evidence on the associations between visual impairment and all-cause dementia and key dementia subtypes will be synthesized narratively and using random effects meta-analysis if appropriate. We will investigate heterogeneity between studies using the x^2 test for homogeneity and I^2 statistic, and meta-regression if appropriate. We will also explore small study effects including publication bias using funnel plots and Egger's statistic if appropriate.

Contacting corresponding authors

Corresponding authors of 26 studies [3-28] were contacted for clarification or additional or not fully reported data. We received additional data or clarification for 11 studies [3-5, 7, 13-16, 19, 23, 25], no response from 14 studies [6, 8, 9, 11, 12, 17, 18, 20-22, 24, 26-28] and for one study [10] the email delivery was unsuccessful.

Supplementary Results

Extended results for visual impairment, glaucoma, age-related macular degeneration (AMD) and diabetic retinopathy

Visual impairment

Ten cohort studies investigated the association between VI and incident all-cause dementia [3, 5, 9, 16, 19, 25, 26, 29, 30, 31] (Supplementary Table 2). The pooled estimate of seven studies [3, 5, 19, 25, 29-31] 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%; Figure 2). After excluding three studies [5, 30, 31] 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 same pattern of results was also observed in a sensitivity analysis with two studies with a global risk of bias rating of moderate [19] or strong [29] (23,312 participants, 2,231 cases, pooled adjusted HR = 1.32, 95% CI: 0.97-1.79, p = 0.08, I^2 = 64.6). Two studies [16, 26] could not be included in the meta-analysis as they did not define VI based on the WHO classification [32]. Results provided by Maruta and colleagues [16] (2,190 participants, 1,153 dementia cases) suggested no association (HR = 1.04, 95% CI: 0.85-1.26] whereas Paik and colleagues [26] (6,029,657 participants, 165,293 dementia cases) reported increased dementia risk in those with mild (HR=1.45, 95% CI: 1.42-1.48), moderate (HR=1.74, 95% CI: 1.70-1.78) and severe VI/blindness (HR=1.75, 95% CI: 1.71-1.79) compared to normal vision. Two studies [3, 9] assessed VI based on contrast sensitivity. The pooled estimate of these two studies [3, 9] was 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 [18, 26, 31] investigated the association with AD (Supplementary Table 2) although one study [18] could not be included in a meta-analysis due to a substantial difference in the definition of exposure that did not include mild VI. The pooled estimate of two studies [26, 31] 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). Results reported by Klaver and colleagues [18] (1,438 participants, 62 AD cases; not included in the meta-analysis) suggested no associations of AD risk with moderate/severe VI (RR =1.01, 95% CI: 0.35-2.88) and with blindness (RR=0.96, 95% CI: 0.68-7.05) compared to normal vision/mild VI, though there was considerable uncertainty around the estimates due to wide CIs (Supplementary Table 2).

Two studies [26, 31] investigated the association with VaD (Supplementary Table 2). The pooled estimate of these two studies [26, 31] 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).

Glaucoma

Eight cohort studies investigated the association between glaucoma and incident all-cause dementia [4, 7, 10, 14, 20, 23, 27, 33] (Supplementary Table 3). The pooled estimate of five studies [7, 14, 20, 27, 33] 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%; Figure 3). A sensitivity analysis with two studies [27, 33] with a global risk of bias rating of moderate revealed the same pattern of results (43,707 participants, 2,472 dementia cases, HR = 1.38, 95% CI: 0.58-3.31, p = 0.47, I^2 = 80.2%). Three studies [4, 10, 23] could not be included in the main analysis: one study [10] due to substantial methodological differences (estimate of effect) and two studies [4, 23] due to use of the same source of data, the Taiwan National Health Insurance Research Database (TNHIRD; Supplementary Table 3). In the study by Helmer and colleagues [10], open-angle glaucoma was associated with significantly increased odds of all-cause dementia compared to no open-angle glaucoma (812 participants, 41 dementia cases, odds ratio = 3.9, 95% CI: 1.5-10.4). The studies based on data from the TNHIRD (32,545 participants, 1,601 dementia cases [23] and 76,585 participants, number of dementia cases not reported [4]) indicated increased dementia risk associated with glaucoma (HR = 1.13, 95% CI: 1.01-1.27), primary open-angle glaucoma (HR = 1.21, 95% CI: 1.02-1.43) [23] and normal tension glaucoma (HR = 1.39, 95% CI: 1.25-1.46) [4] but not with primary angle-closure glaucoma (HR = 1.09, 95% CI: 0.95-1.26) [23]. However, the study by Kuo and colleagues [33] (42,048 participants, 2,304 dementia cases; results for any glaucoma included in the meta-analysis) also based on data from the TNHIRD reported additional results for normal tension glaucoma (HR = 1.17, 95% CI: 0.98-1.40) and angle-closure glaucoma (HR = 0.91, 95% CI: 0.81-1.02) that were statistically not significant. 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 [4, 12, 14, 15, 17, 20, 27, 33] (Supplementary Table 3). The pooled estimate of six studies [12, 14, 17, 20, 27, 33] 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%; Figure 4) compared to no glaucoma. When we excluded studies with a global risk of bias rating of weak, the pooled estimate of four moderate studies [12, 17, 27, 33] also revealed the same pattern of results (2,675,651 participants, 31,747 AD cases, pooled adjusted RR = 1.20, 95% CI: 0.94-1.55, p = 0.15, I^2 = 82.9%). Two studies [4, 15] could not be included in the main analysis due to use of the same source of data (TNHIRD; Supplementary Table 3). In the study by Lin and colleagues [15], primary open-angle glaucoma was associated with an increased AD risk (19,895 participants, 208 AD cases, HR = 1.40, 95% CI: 1.03-1.90). Chen and colleagues [4] (76,585 participants, 3,597 AD cases) reported an association between normal tension glaucoma and AD (HR = 1.52, 95% CI: 1.41-1.63) but found little evidence of an increased risk of AD associated with high tension glaucoma (HR = 1.12, 95% CI: 0.89-1.36). However, the study by Kuo and colleagues [33] (42,048 participants, 183 AD cases; results for any glaucoma included in the meta-analysis) also based on data from the TNHIRD reported additional results for normal tension glaucoma (HR = 0.93, 95% CI: 0.45-1.92) and angle-closure glaucoma (HR = 0.93, 95% CI: 0.62-1.38) that were statistically not significant. In a sensitivity analysis restricting to studies on open-angle glaucoma only, the pooled estimate suggested a reduced risk of AD associated with open-angle glaucoma (168,698 participants, 21,714 AD cases, pooled adjusted HR = 0.91, 95% CI: 0.89-0.94, p<0.001, I^2 = 0.0%) (Supplementary Figure 7). 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 [12, 33] (Supplementary Table 3). 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). Kuo and colleagues [33] (42,048 participants, 1,784 VaD cases; results for open-angle glaucoma included in the meta-analysis) also reported results for any glaucoma (HR = 0.93, 95% CI: 0.85-1.02), normal tension glaucoma (HR = 1.07, 95% CI: 0.87-1.33) and angle-closure glaucoma (HR = 0.90, 95% CI: 0.79-1.02) that were statistically not significant.

Age-related macular degeneration

Five cohort studies reported the association between AMD and incident all-cause dementia [11, 14, 24] (n = 3) and/or AD [6, 11, 14, 18] (n = 4; Supplementary Table 4). Pooled estimates of three studies [11, 14, 24] 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%, Figure 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%, Figure 4). One study [18] (1,438 participants, 62 AD cases) could not be included in the latter meta-analysis, as it investigated severity rather than presence of AMD. The RRs were 1.0 (95% CI: 0.6-1.9) and 1.5 (95% CI: 0.6-3.5) for early and advanced AMD, respectively, in association with AD risk compared to no AMD [18]. In a sensitivity analysis, pooling estimates of two studies with a moderate [11] or strong [6] risk of bias rating also provided no evidence of an association between AMD and AD risk (8,075,197 participants, >7,457 AD cases [exact number cannot be determined], pooled adjusted RR = 1.14, 95% CI: 0.67-1.93, p = 0.64, I^2 = 92.6%).

Diabetic retinopathy

Four studies based on one type 1 diabetic cohort [21], one type 2 diabetic cohort [34] and two cohorts including non-diabetic participants [14, 22] investigated the association between diabetic retinopathy and all-cause dementia with one [22] and two [14, 22] studies, respectively, also investigating VaD and AD. The pooled estimate of four [8, 14, 21, 22] and two studies [14, 22], 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%, Figure 3) and AD (9,955 participants, 1,375 AD cases, pooled adjusted HR = 1.29, 95% CI: 1.03-1.61, p = 0.03, I2 =11.2%, Figure 4) in those with diabetic retinopathy compared to no retinopathy. When we excluded studies with a global risk of bias rating of weak, the pooled estimate of two moderate studies [8, 22] also indicated an increased risk of all-cause dementia associated with diabetic retinopathy (36,039 participants, 5,908 dementia cases, pooled adjusted HR = 1.29, 95% CI: 1.15-1.44, p <0.001, I^2 = 0.0%) Only one study [22] (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). One study [8] (29,961 participants, 5,173 dementia cases) of a type 2 diabetic cohort indicated increased dementia risk in those with proliferative diabetic retinopathy (HR = 1.40, 95% CI: 1.12-1.74) and with diabetic macular edema (HR = 1.42, 95% CI 1.23-1.63; Supplementary Table 6).

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Supplementary Table 1. Quality assessment of included studies

Study	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and drop-outs	Global rating
Brenowitz et al. (2019)	weak	moderate	strong	moderate	weak	weak	weak
Chen et al. (2018)	moderate	moderate	moderate	moderate	weak	moderate	moderate
Choi et al. (2019)	moderate	moderate	strong	moderate	strong	moderate	strong
Davies-Kershaw et al. (2018)	moderate	moderate	weak	moderate	weak	moderate	weak
Ekström & Kilander (2014)	weak	moderate	weak	moderate	weak	weak	weak
Exalto et al. (2014)	strong	moderate	strong	moderate	strong	weak	moderate
Fischer et al. (2016)	strong	moderate	strong	moderate	weak	moderate	moderate
Helmer et al. (2013)	moderate	moderate	strong	moderate	strong	strong	strong
Hwang et al. (2020)	weak	moderate	strong	weak	strong	strong	weak
Keenan et al. (2015)	moderate	moderate	moderate	moderate	weak	moderate	moderate
Keenan et al. (2014)	moderate	moderate	moderate	moderate	weak	moderate	moderate
Klaver et al. (1999)	moderate	moderate	weak	moderate	strong	weak	weak
Kuo et al. (2020)	moderate	moderate	strong	moderate	weak	moderate	moderate
Lai et al. (2014)	moderate	moderate	weak	moderate	weak	moderate	weak
Lee et al. (2019)	weak	moderate	strong	moderate	strong	weak	weak
Lee et al. (2020)	moderate	moderate	strong	moderate	strong	strong	strong

Lin et al. (2014)	moderate	moderate	strong	moderate	weak	moderate	moderate
Maruta et al. (2020)	moderate	moderate	weak	moderate	weak	weak	weak
Moon et al. (2018)	moderate	moderate	strong	moderate	weak	moderate	moderate
Naël et al. (2019)	weak	moderate	strong	moderate	strong	strong	moderate
Nam et al. (2021)	moderate	moderate	weak	moderate	weak	moderate	weak
Ou et al. (2012)	moderate	moderate	weak	moderate	weak	weak	weak
Paik et al. (2020)	moderate	moderate	weak	moderate	weak	moderate	weak
Rodill et al. (2018)	moderate	moderate	weak	moderate	strong	weak	weak
Rogers & Langa (2010)	weak	moderate	strong	moderate	moderate	weak	weak
Schrijvers et al. (2012)	moderate	moderate	strong	moderate	strong	weak	moderate
Su et al. (2016)	moderate	moderate	weak	moderate	weak	moderate	weak
Tran et al. (2020)	weak	moderate	strong	moderate	moderate	weak	weak
Tsai et al. (2015)	moderate	moderate	weak	moderate	weak	moderate	weak
Xiao et al. (2020)	moderate	moderate	strong	moderate	strong	weak	moderate

Supplementary Table 2. Results of included studies for the association between visual impairment and incident all-cause dementia or key dementia subtypes.

Study	Outcome assessment/diagnosis	Visual impairment (VI) assessment/diagnosis	Adjustment	Effect size (95% CI)	*P* value
Brenowitz et al. (2019)	Hospitalization with dementia as primary or secondary diagnosis, dementia medication or at least 1.5 SD decline from baseline in 3MS	Visual acuity of 20/40 or worse measured using corrective lenses with the Bailey-Lovie distance test Contrast sensitivity of <1.55 log units measured using corrective lenses with the Pelli-Robson letter charts	Age, race, sex, education, use of corrective lenses, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, smoking, alcohol use, physical activity	<u>All-cause dementia</u> HR of mild VI to blind[*] = 1.26 (0.90-1.77) HR of contrast sensitivity impairment = 1.11 (0.88-1.38)	0.18[†] 0.38[†]
Davies-Kershaw et al. (2018)	Self- or proxy reported dementia diagnosis, a score <3.5 on IQCODE or dementia medication	Self-reported vision or registered as partially sighted or blind categorized as normal vision (excellent or very good), mild to moderate VI (good or fair), severe VI to blind[*]	Sex, wealth, education, diabetes, hypertension, stroke, smoking[b]	<u>All-cause dementia</u> Aged 50-69: HR of mild to moderate VI[*] = 1.78 (1.04-3.04) HR of severe VI to blind[*] = 3.60 (1.10-11.78) Aged ≥70: HR of mild to moderate VI[*] = 1.22 (0.92-1.64) HR of severe VI to blind[*] = 1.24 (0.69-2.22)	 0.036[†] 0.034[†] NR

					NR
Fischer et al. (2016)	MMSE score of <24 or self- or proxy-reported history of dementia or AD	Contrast sensitivity of <1.55 log units in the better eye measured using Pelli-Robson letter charts	Age, sex, education, smoking, BMI, exercise, alcohol consumption, hypertension, diabetes, number of high inflammatory markers, non-HDL-C, mean IMT, frailty	<u>All-cause dementia</u> HR of contrast sensitivity impairment = 1.96 (1.25-3.07)	NR
Hwang et al. (2020)	Adjudicated, DSM-IV, NINCDS-ADRDA, NINDS-AIREN and AD Diagnostic and Treatment Centers criteria	Self-reported visual impairment defined as not being able to see well enough (with or without glasses) to drive and/or to watch TV and/or to read the newspaper and/or to recognize someone across the room	Age, sex, race, education, income, BMI, alcohol consumption, smoking, physical activity, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, clinic site, treatment status, APOE, hearing impairment	<u>All-cause dementia</u> HR of mild to severe VI = 1.32 (1.02-1.71) <u>AD</u> HR of mild to severe VI = 1.32 (0.97-1.80) <u>VaD</u> HR of mild to severe VI = 1.36 (0.82-2.25)	0.04 0.08 0.23
Klaver et al. (1999)	NINCDS-ADRDA criteria based on clinical/diagnostic evaluation, informant interview and medical records	Best-corrected visual acuity measured at a distance of 3m using a modified Early Treatment Diabetic Retinopathy chart categorized as normal to mild VI ($\geq$0.03), moderate	Age, age^2, gender	<u>AD</u> RR of moderate to severe VI* = 1.01 (0.35-2.88) RR of blindness = 0.96 (0.68-7.05)	NR NR

		to severe VI (≥0.05 and <0.3) and blind (<0.05)[*]			
Lee et al. (2020)	Adjudicated, ICD-10 criteria	Visual acuity measured with corrective lenses using line score from the 20-feet Snellen's E chart; Snellen fractions converted to LogMAR with higher scores indicating poorer visual acuity and categorized as normal vision (<0.3) mild VI (0.3-0.47), moderate VI (0.48-0.99) and severe VI to blind (≥1.00)[*]	Age, sex, education, socioeconomic status, cataract, glaucoma, cardiovascular risk, hearing impairment, poor mobility, depression, physical exercise, intellectual activities, social activities, fruit and vegetable consumption, smoking	All-cause dementia HR of poorer visual acuity = 5.88 (4.04-8.57) HR of mild VI = 1.56 (1.17-2.06) HR of moderate VI = 2.27 (1.68-3.06) HR of severe VI to blindness[*] = 10.84 (6.60-17.81)	<0.001 0.002 <0.001 <0.001
Maruta et al. (2020)	Medical records, based on eligibility assessment for long-term care insurance (questionnaire supplemented by expert committee review taking into account reports from primary care physicians)[‡]	Medical records, based on eligibility assessment for long-term care insurance; visual acuity impairment defined as able to see vision testing chart at a distance of about 1m or in front or very poor eyesight compared to normal vision (no hindrance in daily life)	Age, sex, care-need level, degree of independent daily living	All-cause dementia HR of VI = 1.04 (0.85-1.26)	0.73
Naël et al. (2019)	Adjudicated, DSM-IV and NINCDS-ADRDA criteria	Mild near visual acuity impairment: mild VI:	Age, gender, education, center, hearing loss, living	All-cause dementia	

		Parinaud 3 or 4 (Snellen equivalent 20/30-20/60), moderate near visual acuity impairment to blind: Parinaud >4 (Snellen equivalent <20/60)[a]; self-reported distance visual function loss defined as inability or difficulty in recognizing a familiar face at 4 meters with corrective lenses	alone, income, depressive symptoms, smoking, BMI, hypertension, stroke history, history of cardiovascular disease, hypercholesterolemia, hypertriglyceridemia, diabetes, APOE e4	HR of mild VI = 1.14 (0.90-1.43)[†]	0.28[†]
				HR of moderate VI to blindness[*] = 1.40 (1.05-1.86)[†]	0.02[†]
				HR of severe distance visual function loss = 1.30 (0.99-1.70)[†]	0.06[†]
				<2 years follow-up:	
				HR of mild VI = 1.63 (1.06-2.51)	
				HR of moderate VI to blindness[*] = 1.95 (1.16-3.28)	0.027
				HR of severe distance visual function loss = 1.12 (0.63-1.99)	0.012
				2-4 years follow-up:	
				HR of mild VI = 1.15 (0.71-1.86)	0.70
				HR of moderate VI to blindness[*] = 1.82 (1.07-3.08)	
					0.57

53

				HR of severe distance visual function loss = 1.22 (0.70-2.13)	0.027
				≥4 years follow-up:	
				HR of mild VI = 1.00 (0.77-1.31)	0.48
				HR of moderate VI to blindness[*] = 1.34 (0.95-1.89)	
				HR of severe distance visual function loss = 1.49 (1.11-2.00)	0.99
					0.095
					0.008
Paik et al. (2020)	Medical records, ICD-10: F00, G30, F01, F02, F03, G23.1, G31.0, G31.1, G31.82, G31.83, G31.88, F10.7 for all-cause dementia, F00 and G30 for AD, and F01 for VaD	Measured best-corrected visual acuity of the worse eye categorized as <0.1 (severe VI to blind), <0.3 (moderate VI), <1.0 (mild VI) or ≥1.0 (normal vision)[*];	Age, sex, smoking, alcohol consumption, physical activity, diabetes, hypertension, lipid levels	All-cause dementia HR of mild VI[*] = 1.45 (1.42-1.48) HR of moderate VI[*] = 1.74 (1.70-1.78)	NR NR

				HR of severe VI to blindness* = 1.75 (1.71-1.79)	NR
				AD	
				HR of mild VI* = 1.47 (1.44-1.51)	NR
				HR of moderate VI* = 1.75 (1.70-1.80)	NR
				HR of severe VI to blindness* = 1.75 (1.70-1.80)	NR
				VaD	
				HR of mild VI* = 1.40 (1.33-1.47)	NR
				HR of moderate VI* = 1.73 (1.63-1.85)	NR
				HR of severe VI to blindness* = 1.79 (1.68-1.91)	NR
					NR

Rogers & Langa (2009)	Adjudicated, DSM-III-R and DSM-IV criteria	Self-reported vision categorized as normal vision (excellent or very good) or mild to severe VI or blind (good or fair or poor or blind) vision	Age, gender, race, education, APOE e4, head injury, diabetes, hypertension, stroke, heart disease	All-cause dementia RR of mild to severe VI or blind vision = 2.70 (1.25-5.56)§	0.014
Tran et al. (2020)	Adjudicated, DSM-IV criteria	Nonpinhole visual acuity of 20/40 or worse in at least 1 eye; self-reported moderate to severe VI* based on a visual function questionnaire	Age, race, hormone therapy, education, physical activity, hearing loss, smoking, baseline 3MS score, depression, cardiovascular disease, congestive heart failure, hypertension, hyperlipidemia, chronic pulmonary disease, peptic ulcer disease, liver disease, leukemia or lymphoma, diabetes	All-cause dementia HR of mild VI to blindness* = 2.14 (1.08-4.21) HR of moderate to severe VI* = 1.22 (0.56-2.66)	0.03 0.61

AD, Alzheimer's disease; BMI, body mass index; CI, confidence interval; DSM-III-R, Diagnostic and Statistical Manual of Mental disorders, Third Edition, Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HR, hazard ratio; ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; IMT, intima-media thickness, IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; LogMAR, Logarithm of the Minimum Angle of Resolution; MMSE, Mini-Mental State Examination; non-HLC-C, NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences; non-high-density lipoprotein cholesterol; NR, not reported; RR, risk ratio; SD, standard deviation; 3MS, Modified Mini-Mental State Examination; VI, visual impairment; 3MS, Modified Mini-Mental State Examination;

* Description of categories based on the WHO definition of visual impairment [32] to enable comparability with other studies

†Additional information provided by the authors

‡As previously described [34, 35]

§Comparison group reversed for comparability of results; better vision reported as normal and worse vision described as mild to poor/blind to allow comparisons with other studies; better versus worse vision: RR = 0.37 (0.18-0.80)

Supplementary Table 3. Results of included studies for the association between glaucoma and incident all-cause dementia or key dementia subtypes.

Study	Outcome assessment/diagnosis	Glaucoma assessment/diagnosis	Adjustment	Effect size (95% CI)	*P* value
Chen et al. (2018)	Medical records, ICD-9-CM: 290.x, 291.2, 292.82, 294.x, 331.0 for all-cause dementia[*] and 331.0 for AD	Medical records, ICD-9-CM: 365.12 for NTG and 365.11 for HTG[*]	Age, sex, diabetes, hypertension, hyperlipidemia, coronary artery disease, stroke	All-cause dementia HR of NTG = 1.39 (1.25 – 1.46) AD HR of NTG = 1.52 (1.41-1.63) HR of HTG = 1.12 (0.89-1.36)	<0.0001 <0.0001 0.38[*]
Ekström & Kilander (2013)	Medical records, NINCDS-ADRDA criteria	Presence of a reproducible visual field defect on eye examination	Age, sex, deaths, pseudoexfoliation	All-cause dementia HR of OAG = 1.09 (0.69-1.74)	0.71[*]
Helmer et al. (2013)	Adjudicated, DSM-IV criteria	Adjudicated based on eye examination	Age, sex, education, hypertension, diabetes, history of cardiovascular ischemic disease, stroke history, familial history of glaucoma, APOE e4	All-cause dementia OR of OAG = 3.9 (1.5-10.4)	0.0054

Keenan et al. (2015)	Medical records, ICD-10: F00, G30 for AD and F01 for VaD	Medical records, ICD-10: H40.1	Age, sex, calendar year of admission, region of residence, socioeconomic status	AD SRR of POAG = 1.01 (0.96-1.06) VaD SRR of POAG = 1.10 (1.05-1.16)	NR NR
Kuo et al. (2020)	Medical records, diagnoses of AD, VaD, and Parkinson's disease with concurrent dementia according to ICD-9/ICD-10 codes	Medical records diagnosis of glaucoma made by an ophthalmologist according to ICD-9/ICD-10 codes	Age, gender, education, marital status, hypertension, diabetes, ischemic heart disease, hyperlipidemia, congestive heart failure, peripheral vascular disease, cerebrovascular disease, sensorineural hearing loss, AMD, hemiplegia or paraplegia	All-cause dementia HR of any glaucoma = 0.96 (0.89-1.04) HR of OAG = 0.87 (0.76-1.00) HR of NTG = 1.17 (0.98-1.40) HR of ACG = 0.91 (0.81-1.02) AD HR of any glaucoma = 1.02 (0.76-1.36) HR of OAG = 0.83 (0.49-1.39) HR of NTG = 0.93 (0.45-1.92)	0.3443 NR NR NR 0.9025 NR

				HR of ACG = 0.93 (0.62-1.38)	NR
				VaD	NR
				HR of any glaucoma = 0.93 (0.85-1.02)	
				HR of OAG = 0.83 (0.71-0.98)	0.1154
				HR of NTG = 1.07 (0.87-1.33)	
				HR of ACG = 0.90 (0.79-1.02)	NR
					NR
					NR
Lee et al. (2019)	Adjudicated, DSM-IV and NINCDS-ADRDA criteria	Medical records, ICD-9: 365.1*	Age, sex, education, race, APOE e4, smoking, AMD, diabetic retinopathy	All-cause dementia HR of glaucoma = 1.04 (0.89, 1.22) *	0.601*
				HR of glaucoma (0-5 yrs) = 1.32 (1.02-1.72)	0.04
				HR of glaucoma (>5 yrs) = 1.00 (0.84-1.20)	0.99

				AD HR of glaucoma = 0.95 (0.80-1.14) HR of glaucoma (0-5 yrs) = 1.46 (1.08-1.91) HR of glaucoma (>5 yrs) = 0.87 (0.71-1.07)	0.61 0.013 0.19
Lin et al. (2014)	Medical records, ICD-9-CM: 365.10, 365.11, 365.12,	Medical records, ICD-9-CM diagnoses	Age, sex, hypertension, diabetes, heart failure, stroke, insurance eligibility group, income, diagnostic year, urbanization level, CCI	AD HR of POAG = 1.40 (1.03-1.90)	0.033
Moon et al. (2018)	Medical records, KCD: F009, G300, G301, G308, G309	Medical records, KCD: H401, E6691 and prescribed glaucoma medication	Age, sex, residential area, income, CCI, hypertension, diabetes, hyperlipidemia, ischemic stroke	AD HR of POAG = 1.40 (1.18-1.67) HR of POAG (aged <65) = 1.17 (0.90-1.52) HR of POAG (aged ≥65) = 1.75 (1.40-2.17)	<0.001 NR NR
Ou et al. (2012)	Medical records, ICD-9-CM: 331.0 for AD and 290, 290.0-4, 290.8-9, 291.0, 291.2, 292.82,	Medical records, ICD-9-CM: 365.1, 365.10, 365.11, 365.12, 365.15	Age, sex, race, CCI, dry AMD, wet AMD, unspecified AMD, background DR,	All-cause dementia	NR

	294.0-1, 294.8, 331.1-2, 331.7, 331.82, 797.xx for other dementia		proliferative DR, vitreous hemorrhage, cataract, pseudophakia/aphakia, cataract surgery	HR of OAG = 0.93 (0.91-0.95) AD HR of OAG = 0.91 (0.88-0.93)	NR
Su et al. (2016)	Medical records, ICD-9-CM: 290, 294.1, 331.0	Medical records, ICD-9-CM: 365.1 for POAG and 365.2 for PACG	Age, gender, hypertension, diabetes, coronary artery disease, hyperlipidemia, head injury	All-cause dementia HR of glaucoma = 1.13 (1.01-1.27) HR of POAG = 1.21 (1.02-1.43) HR of PACG = 1.09 (0.95-1.26)	0.03[*] 0.03[*] 0.23[*]
Xiao et al. (2020)	Adjudicated, DSM-IV and NINCDS-ADRDA criteria	Self-reported and confirmed by participants' medical records	Age, sex, education, APOE e4, baseline MMSE, smoking, alcohol consumption, hypertension, diabetes, BMI, depression, heart disease, cataract	All-cause dementia HR of glaucoma = 2.38 (1.08-5.23) AD HR of glaucoma = 2.77 (1.17-6.56)	0.03 0.02

ACG, angle-closure glaucoma; AD, Alzheimer's disease; AMD, age-related macular degeneration; APOE, apolipoprotein; CCI, Charlson comorbidities index; CI, confidence interval; DR, diabetic retinopathy; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HR, hazard ratio; HTG, high tension glaucoma; ICD-8, International Classification of Diseases, Eighth Revision; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Classification of Diseases, Tenth Revision; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; KCD, Korean Classification of Diseases; MMSE, Mini-Mental State Examination; NR, not reported; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related

Disorders Association; NTG, normal tension glaucoma; OAG, open-angle glaucoma; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma; SRR, standardized rate ratio; VaD, vascular dementia; yrs, years;

[*]Additional information provided by the authors

Supplementary Table 4. Results of included studies for the association between age-related macular degeneration and incident all-cause dementia or key dementia subtypes

Study	Outcome assessment/diagnosis	Visual impairment assessment/diagnosis	Adjustment	Effect size (95% CI)	*P* value
Choi et al. (2019)	Medical records, ICD-10: F00, G30	Medical records, ICD-10: H35.3	Age, sex, household income, smoking, alcohol consumption, physical activity, BMI, systolic blood pressure, fasting serum glucose, total cholesterol, CCI	AD HR of AMD = 1.48 (1.25-1.74)	NR
Keenan et al. (2014)	Medical records	Medical records	Age, sex, calendar year of admission, region of residence, socioeconomic status	All-cause dementia SRR of AMD = 0.91 (0.79-1.04) AD SRR of AMD = 0.86 (0.67-1.08)	0.19 0.22
Klaver et al. (1999)	NINCDS-ADRDA criteria based on clinical/diagnostic evaluation, informant interview and medical records	Ophthalmologic screening examination, diagnosis based on grading of fundus transparencies	Age, age^2, gender, smoking, atherosclerosis	AD RR of AMD (stage 1 or 2) = 1.0 (0.6-1.9) RR of AMD (stage 3 or 4) = 1.5 (0.6-3.5)	NR NR

Lee et al. (2019)	Adjudicated, DSM-IV and NINCDS-ADRDA criteria	Medical records, ICD-9: 362.50, 362.51, 362.52	Age, sex, education, race, APOE e4, smoking, glaucoma, DR	All-cause dementia HR of AMD = 1.16 (1.01, 1.34)*	0.038*
				HR of AMD (0-5 yrs) = 1.25 (1.03-1.53)	0.03
				HR of AMD (>5 yrs) = 1.39 (1.18-1.65) AD	<0.001
				HR of AMD =1.20 (1.02-1.40)	
				HR of AMD (0-5 yrs) = 1.20 (0.95-1.50)	0.03
				HR of AMD (>5 yrs) = 1.50 (1.25-1.81)	0.12
					<0.001
Tsai et al. (2015)	Medical records, ICD-9-CM: 331.0, 290.xx	Medical records, ICD-9-CM: 362.50, 362.51, 362.52	Age[†], sex[†], time of enrolment[†], Parkinson's disease, hypertension, diabetes, dysrhythmia, coronary artery disease, hyperlipidemia, number of insurance claims for outpatients' visits	All-cause dementia HR of AMD = 1.44 (1.26-1.64)	<0.001
				HR of exudative AMD = 1.35 (0.89-2.06)	0.163
				HR of nonexudative AMD = 1.44 (1.26-1.65)	<0.001

AMD, age-related macular degeneration; BMI, body mass index; CI, confidence interval; CCI, Charlson comorbidity index; DR, diabetic retinopathy; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HR, hazard ratio; ICD-9, International Classification of Disease, Ninth Revision; ICD-10, International Classification of Disease, Tenth Revision; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NR, not reported; OAG, open-angle glaucoma; RR, risk ratio; SRR, standardized rate ratio; yrs, years;

[*]Additional information provided by the authors

[†]Participants with and without AMD matched for age, sex and time of enrolment

Supplementary Table 5. Results of included studies for the association between cataract diagnosis and incident all-cause dementia or key dementia subtypes

Study	Outcome assessment/diagnosis	Visual impairment assessment/diagnosis	Adjustment	Effect size (95% CI)	*P* value
Ekström & Kilander (2013)	Medical records, NINCDS-ADRDA criteria	Presence of cataract on eye examination	Age, sex	All-cause dementia SRR of cataract = 1.14 (0.83-1.58)	NR
Lai et al. (2014)	Medical records, ICD-9: 331.0	Medical records, ICD-9: 366	Age, sex, diabetes, head injury, hypertension	AD HR of cataract = 1.43 (1.13-1.82)	0.0032[*]
Lee et al. (2019)	Adjudicated, DSM-IV and NINCDS-ADRDA criteria	Medical records, ICD-9: 366.*	Age, sex, education, race, APOE e4, smoking, glaucoma, AMD, diabetic retinopathy	All-cause dementia HR of cataract = 1.17 (0.94, 1.47)[*] AD HR of cataract = 1.13 (0.88, 1.45)[*] HR of cataract (0-5 yrs) = 0.99 (0.73-1.32) HR of cataract (>5 yrs) = 1.21 (0.93-1.57)	0.167[*] 0.345[*] 0.92 0.15

Xiao et al. (2020)	Adjudicated, DSM-IV and NINCDS-ADRDA criteria	Self-reported and confirmed by participants' medical records	Age, sex, education, APOE e4, baseline MMSE, smoking, alcohol consumption, hypertension, diabetes, BMI, depression, heart disease, glaucoma	<u>All-cause dementia</u> HR of cataract = 1.23 (0.85-1.79) <u>AD</u> HR of cataract = 1.14 (0.73-1.77)	0.28 0.57

AMD, age-related macular degeneration; APOE, apolipoprotein; BMI, body mass index; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HR, hazard ratio; ICD-8, International Classification of Disease, Eighth Revision; ICD-9, International Classification of Diseases, Ninth Revision; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MMSE, Mini-Mental State Examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; SRR, standardized rate ratio; yrs, years;

[*]Additional information provided by the authors

Supplementary Table 6. Results of included studies for the association between diabetic retinopathy and incident all-cause dementia or key dementia subtypes

Study	Outcome assessment/diagnosis	Visual impairment assessment/diagnosis	Adjustment	Effect size (95% CI)	*P* value
Exalto et al. (2014)	Medical records, ICD-9: 290.0, 331.0, 290.4x, 290.1, 290.0, 290.1x, 331.0, 290.1x, 290.2x, 290.3, 290.4x	Medical record, ICD-9: 250.5, 362.02 for DPR and 250.5, 362.53, 250.5, 362.83 for DME	Age, sex, race, education, medical utilization, composite measures of diabetes severity and vascular disease, BMI, smoking Age, gender, race, education, medical utilization, diabetic medication use	All-cause dementia HR of DR = 1.32 (1.17-1.49) HR of proliferative DR = 1.40 (1.12-1.74) HR of DME = 1.42 (1.23-1.63)	NR NR NR
Lee et al. (2019)	Adjudicated, DSM-IV and NINCDS-ADRDA criteria	Medical records, ICD-9: 362.50, 362.51, 362.52	Age, sex, education, race, APOE e4, smoking, glaucoma, AMD	All-cause dementia HR of DR = 1.80 (1.41, 2.29)[*] HR of DR (0-5 yrs) = 1.96 (1.31-2.96) HR of DR (>5 yrs) = 1.87 (1.39-2.51)	<0.001[*] 0.001

				AD	<0.001
				HR of DR = 1.44 (1.08-1.94)	
				HR of DR (0-5 yrs) = 1.67 (1.01-2.74)	0.02
				HR of DR (>5 yrs) = 1.50 (1.05-2.15)	0.045
					0.027
Rodill et al. (2018)	Medical records, ICD-9: 331.0, 290.4x, 290.0, 291.1x, 290.2x, 290.3, 294.1x, 294.2x, 294.8	Medical records, ICD-9:362.02, 362.07, 362.53, 362.83, 250.5x, 362.0x and CPT-4: 67228, 67208, 67210	Age, sex, race, glycosylated hemoglobin, neuropathy, diabetic nephropathy, end-stage renal disease, cardiovascular disease, stroke, hyperglycemic or hypoglycemic episodes	All-cause dementia HR of DR = 1.12 (0.82-1.54)	NR
Schrijvers et al. (2012)	Adjudicated, DSM-III-R, NINCDS-ADRDA and NINDS-AIREN criteria	Ophthalmologic examination, presence of ≥1dot/blot hemorrhages, microaneurysms, or cotton wool spots or evidence of laser treatment for retinopathy	Age, sex, stroke, SBP, antihypertensive medication, education, APOE e4, smoking, diabetes, total cholesterol, CRP, coronary heart disease	All-cause dementia HR of DR = 1.15 (0.89-1.50)	NR
				AD HR of DR = 1.15 (0.86-1.55)	NR
				VaD	NR

				HR of DR = 0.90 (0.39-2.11)	

AMD, age-related macular degeneration; CI, confidence interval; CPT-4, Current Procedural Terminology, 4th edition; CRP, C-reactive protein; DME, diabetic macular edema; DR, diabetic retinopathy; DSM-III-R, Diagnostic and Statistical Manual of Mental disorders, Third Edition, Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HR, hazard ratio; ICD-9, International Classification of Disease, Ninth Revision; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological and Communicative Disorders and Stroke – Association Internationale pour la Recherché et l'Enseigment en Neurosciences; NR, not reported; OAG, open-angle glaucoma; SBP, systolic blood pressure;

[*] Additional information provided by the authors

Supplementary Table 7. Results of included studies for the association between other eye conditions and incident all-cause dementia or key dementia subtypes

Study	Outcome assessment/diagnosis	Visual impairment assessment/diagnosis	Adjustment	Effect size (95% CI)	*P* value
Nam et al. (2021)	Medical records, ICD-10-CM code F00 and/or G30 and a prescription for donepezil, rivastigmine, galantamine and/or memantine for AD; ICD-10-CM code F01 and a prescription for medication for VaD; NINDS-AIREN criteria	Medical record, ICD-10-CM code H34.8 for central retinal vein occlusion or 362.36 for venous tributary occlusion	Age, sex, smoking, alcohol consumption, physical activity, BMI, hypertension, diabetes, dyslipidemia	All-cause dementia HR of RVO = 1.16 (1.12-1.21) AD HR of RVO = 1.15 (1.11-1.20) VaD HR of RVO = 1.24 (1.12-1.37)	NR NR NR

AD, Alzheimer's disease; BMI, body mass index; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; NINDS-AIREN, National Institute of Neurological and Communicative Disorders and Stroke – Association Internationale pour la Recherché et l'Enseigment en Neurosciences; RVO, retinal vein occlusion; VaD, vascular dementia;

1   exp Vision/ (27341)

2   vision.ti,ab. (109239)

3   (visual adj (function$ or acuity)).ti,ab. (69747)

4   exp Vision Disorders/ (70736)

5   exp Refractive Errors/ (32169)

6   (presbyop$ or myop$ or astigmati$ or hyperop$).ti,ab. (60460)

7   exp Diabetic Retinopathy/ (23909)

8   diabetic retinopath$.ti,ab. (21700)

9   exp Hypertensive Retinopathy/ (172)

10   hypertensive retinopath$.ti,ab. (622)

11   exp Retinal Artery Occlusion/ (2242)

12   exp Retinal Vein Occlusion/ (4083)

13   (retina$1 adj3 occlu$).ti,ab. (7730)

14   exp Retinal Degeneration/ (41251)

15   (retina$1 adj3 degenerat$).ti,ab. (10185)

16   (macular adj3 degenerat$).ti,ab. (19534)

17   exp Retinal Hemorrhage/ (5177)

18   retina$1 hemorrhage$1.ti,ab. (1754)

19   (armd or amd).ti,ab. (12683)

20   exp Cataract/ (28455)

21   cataract.ti,ab. (46718)

22   (visual$ adj3 impair$).ti,ab. (16022)

23   exp Glaucoma/ (51596)

24   glaucoma.ti,ab. (55325)

25   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or
21 or 22 or 23 or 24 (432503)

26   exp Dementia/ (160636)

27   exp Alzheimer Disease/ (90897)

28   *dementia, vascular/ or *dementia, multi-infarct/ or *frontotemporal dementia/ or *primary progressive
nonfluent aphasia/ (6357)

29   dement$.ti,ab. (108310)

30   alzheimer$.ti,ab. (138948)

31   ((vascular or frontotemporal) adj dementia).ti,ab. (11808)

32   26 or 27 or 28 or 29 or 30 or 31 (245778)

33   prospective$.ti,ab. (674356)

34   longitudinal.ti,ab. (234819)

35   *Longitudinal Studies/ (1822)

36   *Prospective Studies/ (390)

37   predict$.ti,ab. (1511606)

38   inciden$.ti,ab. (851157)

39   determinant$1.ti,ab. (227114)

40   hazard$1.ti,ab. (212995)

41   risk.ti,ab. (2001927)

42   33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 (4482544)
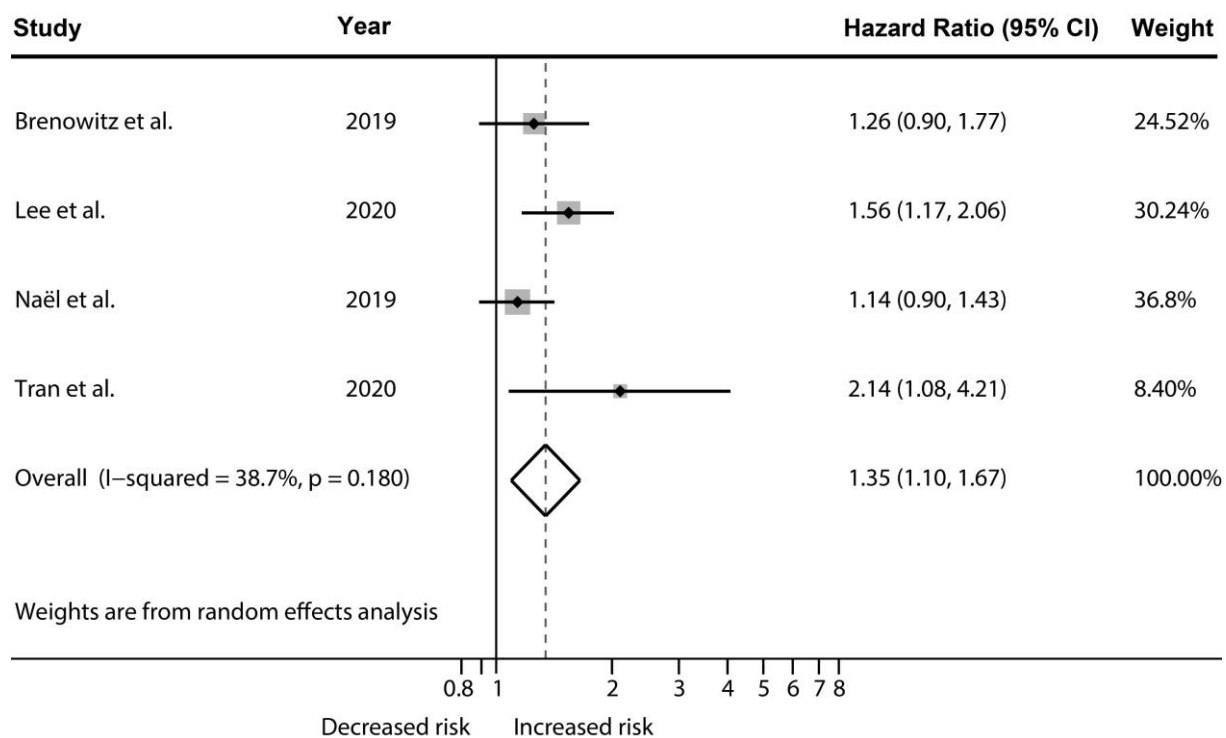
43   25 and 32 and 42 (861)

Supplementary Figure 1. Search strategy in Medline

1   exp vision/ (254619)
2   vision.ti,ab. (148236)
3   (visual adj (function$ or acuity)).ti,ab. (91032)
4   exp visual disorder/ (227581)
5   exp refraction error/ (49630)
6   (presbyop$ or myop$ or astigmati$ or hyperop$).ti,ab. (76449)
7   exp diabetic retinopathy/ (40958)
8   diabetic retinopath$.ti,ab. (30108)
9   exp hypertension retinopathy/ (1264)
10   hypertensive retinopath$.ti,ab. (845)
11   exp retina artery occlusion/ (5003)
12   exp retina vein occlusion/ (8442)
13   (retina$1 adj3 occlu$).ti,ab. (10074)
14   exp retina degeneration/ (39552)
15   (retina$1 adj3 degenerat$).ti,ab. (13374)
16   (macular adj3 degenerat$).ti,ab. (26499)
17   exp retina hemorrhage/ (8288)
18   retina$1 hemorrhage$1.ti,ab. (2306)
19   (armd or amd).ti,ab. (18728)
20   exp cataract/ (56717)
21   cataract.ti,ab. (54611)
22   exp visual impairment/ (94245)
23   (visual$ adj3 impair$).ti,ab. (22450)
24   exp glaucoma/ (80573)
25   glaucoma.ti,ab. (65616)
26   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or
21 or 22 or 23 or 24 or 25 (699521)
27   exp dementia/ (349154)
28   exp Alzheimer disease/ (194250)
29   exp multiinfarct dementia/ (11992)
30   *frontal variant frontotemporal dementia/ or *primary progressive aphasia/ (2236)
31   dement$.ti,ab. (158896)
32   alzheimer$.ti,ab. (192959)
33   ((vascular or frontotemporal) adj dementia).ti,ab. (18311)
34   27 or 28 or 29 or 30 or 31 or 32 or 33 (400689)
35   prospective$.ti,ab. (1037368)
36   longitudinal.ti,ab. (315334)
37   *prospective study/ (23152)
38   *longitudinal study/ (7189)
39   predict$.ti,ab. (2034052)
40   inciden$.ti,ab. (1197569)
41   determinant$1.ti,ab. (274923)
42   hazard$1.ti,ab. (304006)
43   risk.ti,ab. (2913315)
44   35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 (6172643)
45   26 and 34 and 44 (3021)

**Supplementary Figure 2. Search strategy in Embase**

1   exp Vision/ (15506)
2   vision.ti,ab. (44413)
3   (visual adj (function$ or acuity)).ti,ab. (5928)
4   exp Vision Disorders/ (16685)
5   exp Refraction Errors/ (547)
6   (presbyop$ or myop$ or astigmati$ or hyperop$).ti,ab. (3685)
7   diabetic retinopath$.ti,ab. (344)
8   hypertensive retinopath$.ti,ab. (8)
9   (retina$1 adj3 occlu$).ti,ab. (84)
10   (retina$1 adj3 degenerat$).ti,ab. (655)
11   (macular adj3 degenerat$).ti,ab. (597)
12   retina$1 hemorrhage$1.ti,ab. (61)
13   (armd or amd).ti,ab. (388)
14   exp Cataracts/ (303)
15   cataract.ti,ab. (559)
16   (visual$ adj3 impair$).ti,ab. (6803)
17   exp Glaucoma/ (451)
18   glaucoma.ti,ab. (902)
19   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (74140)
20   exp Dementia/ (74758)
21   exp Alzheimer's Disease/ (45292)
22   exp vascular dementia/ (2073)
23   exp semantic dementia/ (1906)
24   dement$.ti,ab. (63793)
25   alzheimer$.ti,ab. (57660)
26   ((vascular or frontotemporal) adj dementia).ti,ab. (6442)
27   20 or 21 or 22 or 23 or 24 or 25 or 26 (99711)
28   prospective$.ti,ab. (66174)
29   longitudinal.ti,ab. (108129)
30   *longitudinal studies/ (2952)
31   *prospective studies/ (94)
32   predict$.ti,ab. (436974)
33   inciden$.ti,ab. (77906)
34   determinant$1.ti,ab. (51052)
35   hazard$1.ti,ab. (17471)
36   risk.ti,ab. (338831)
37   28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (898379)
38   19 and 27 and 37 (303)

Supplementary Figure 3. Search strategy in PsycINFO

Study	Year		Hazard Ratio (95% CI)	Weight
Brenowitz et al.	2019		1.26 (0.90, 1.77)	24.52%
Lee et al.	2020		1.56 (1.17, 2.06)	30.24%
Naël et al.	2019		1.14 (0.90, 1.43)	36.8%
Tran et al.	2020		2.14 (1.08, 4.21)	8.40%
Overall (I−squared = 38.7%, p = 0.180)			1.35 (1.10, 1.67)	100.00%

Weights are from random effects analysis

0.8 1   2   3   4 5 6 7 8

Decreased risk   Increased risk

Supplementary Figure 4. Meta-analysis of hazard ratios of at least mild visual impairment compared to normal vision on incident all-cause dementia excluding three studies assessing self-reported vision
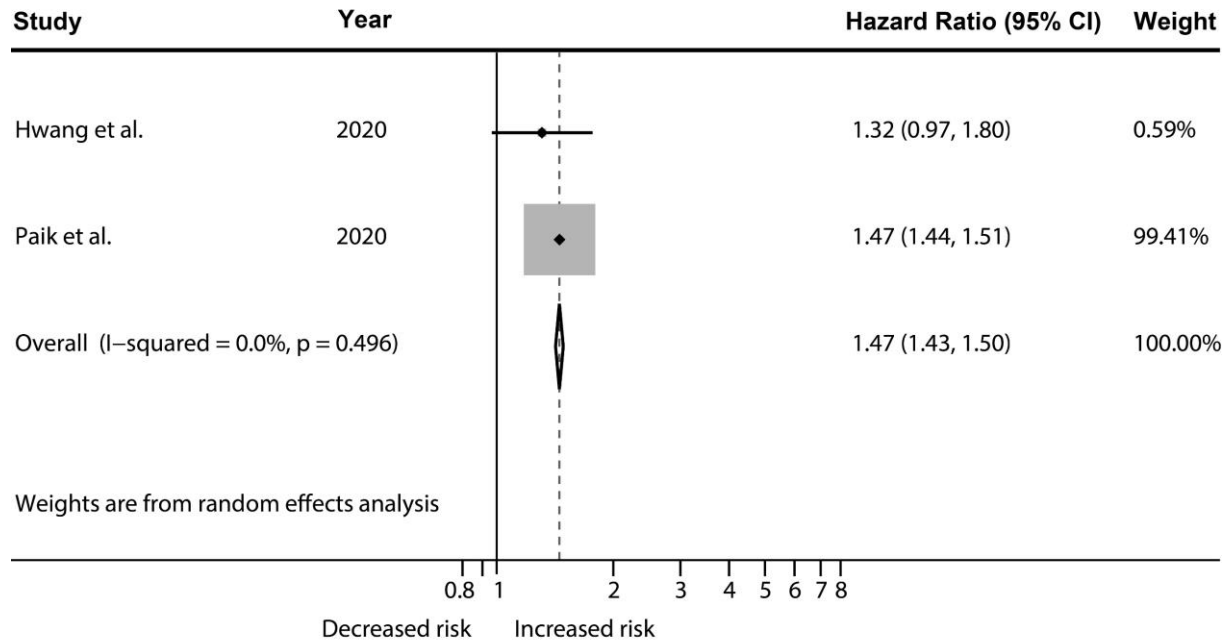
Abbreviations: CI, confidence interval
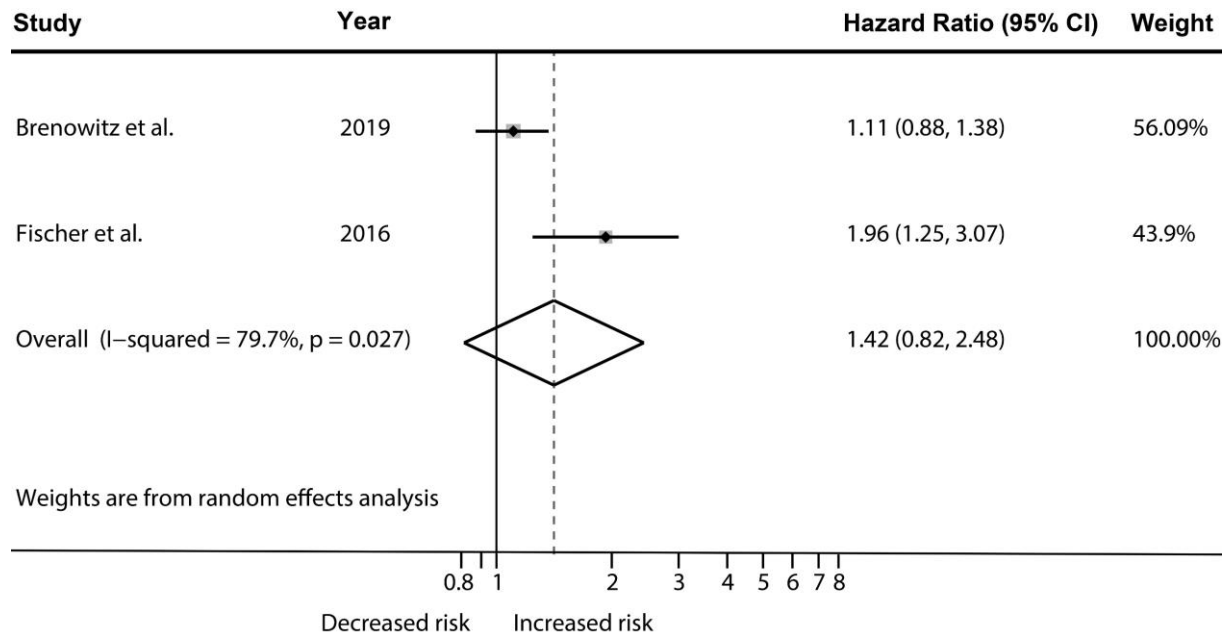
Supplementary Figure 5. Meta-analysis of hazard ratios of low contrast sensitivity compared to normal contrast sensitivity on incident all-cause dementia

Abbreviations: CI, confidence interval

A. Alzheimer's disease

B. Vascular dementia
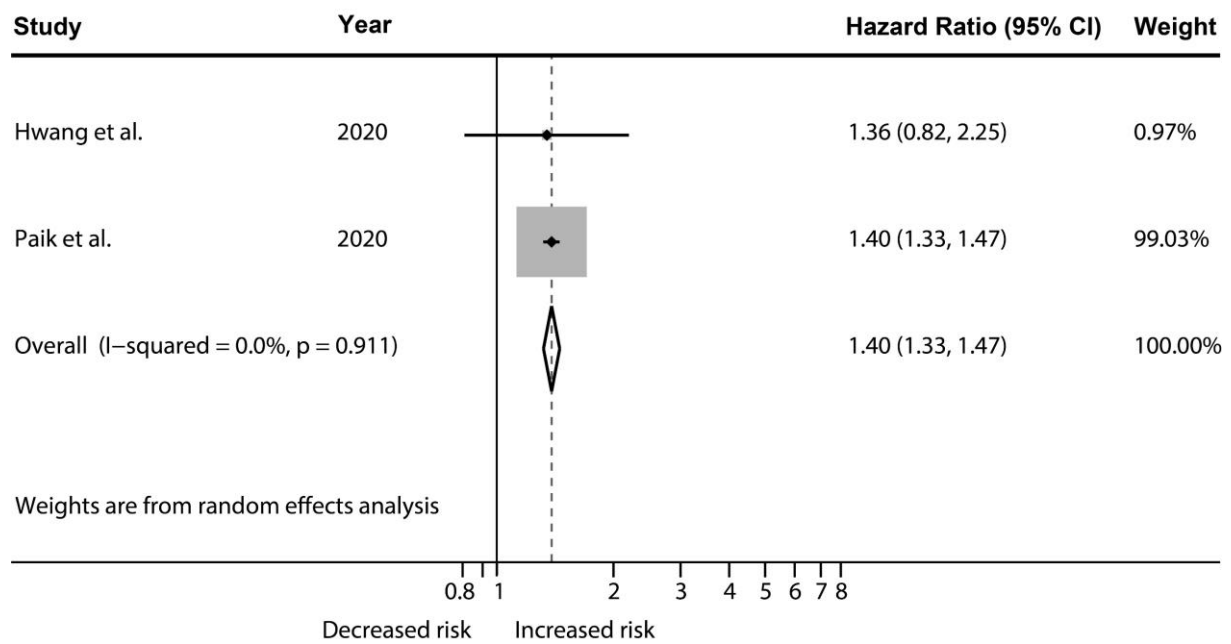
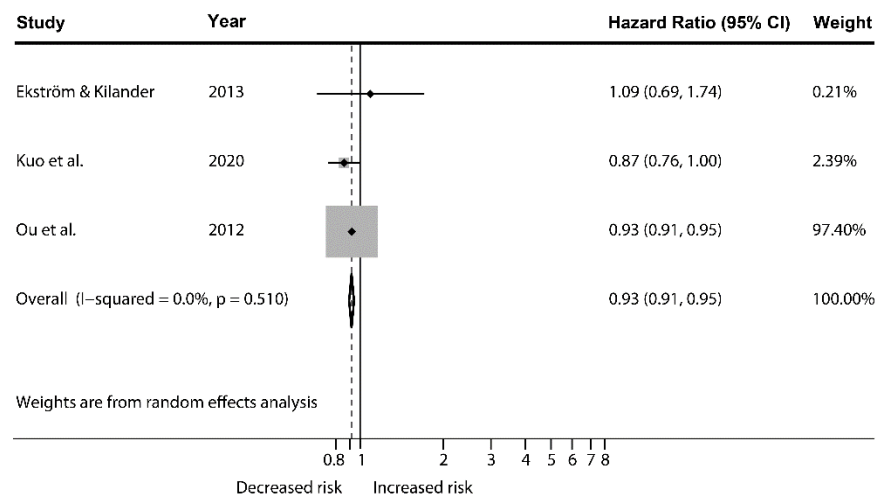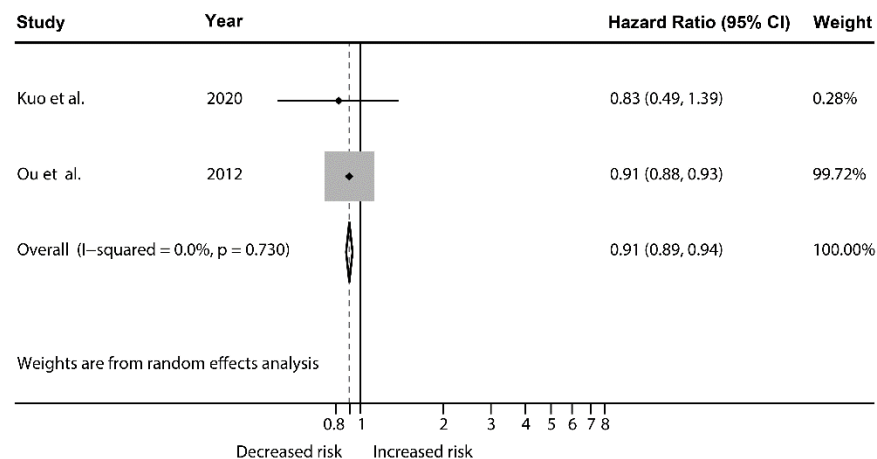**Supplementary Figure 6. Meta-analysis of hazard ratios of mild to severe visual impairment compared to normal vision on incident Alzheimer's disease (A) and vascular dementia (B)**

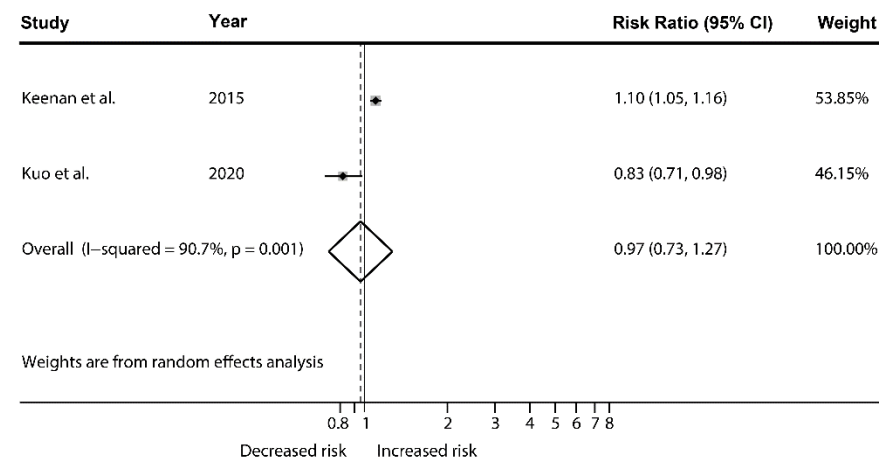Abbreviations: CI, confidence interval

A. All-cause dementia

Study	Year		Hazard Ratio (95% CI)	Weight
Ekström & Kilander	2013		1.09 (0.69, 1.74)	0.21%
Kuo et al.	2020		0.87 (0.76, 1.00)	2.39%
Ou et al.	2012		0.93 (0.91, 0.95)	97.40%
Overall (I–squared = 0.0%, p = 0.510)			0.93 (0.91, 0.95)	100.00%

Weights are from random effects analysis

0.8 1   2   3   4   5 6 7 8

Decreased risk   Increased risk

C. Vascular dementia

Study	Year		Risk Ratio (95% CI)	Weight
Keenan et al.	2015		1.10 (1.05, 1.16)	53.85%
Kuo et al.	2020		0.83 (0.71, 0.98)	46.15%
Overall (I–squared = 90.7%, p = 0.001)			0.97 (0.73, 1.27)	100.00%

Weights are from random effects analysis

0.8 1   2   3   4   5 6 7 8

Decreased risk   Increased risk

B. Alzheimer's disease

Study	Year		Hazard Ratio (95% CI)	Weight
Kuo et al.	2020		0.83 (0.49, 1.39)	0.28%
Ou et al.	2012		0.91 (0.88, 0.93)	99.72%
Overall (I–squared = 0.0%, p = 0.730)			0.91 (0.89, 0.94)	100.00%

Weights are from random effects analysis
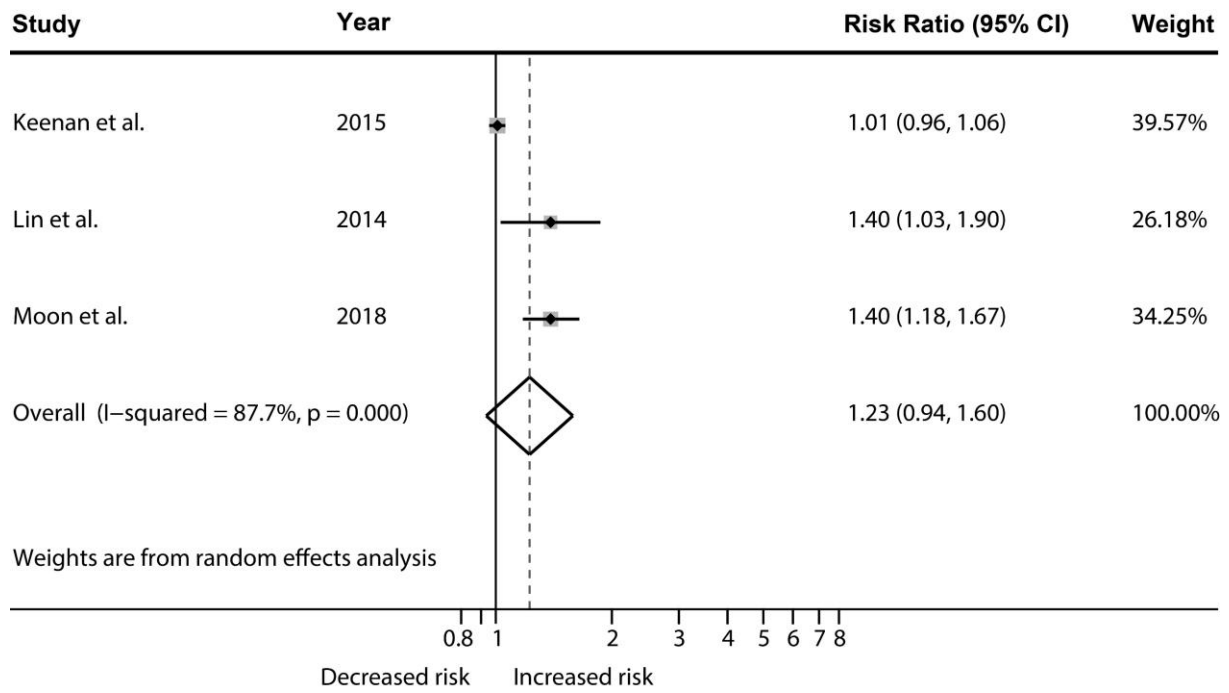
0.8 1   2   3   4   5 6 7 8

Decreased risk   Increased risk

Supplementary Figure 7. Meta-analysis of risk ratios of open-angle glaucoma compared to no open-angle glaucoma on incident all-cause dementia, Alzheimer's disease and vascular dementia

Abbreviations: CI, confidence interval

Study	Year		Risk Ratio (95% CI)	Weight
Keenan et al.	2015		1.01 (0.96, 1.06)	39.57%
Lin et al.	2014		1.40 (1.03, 1.90)	26.18%
Moon et al.	2018		1.40 (1.18, 1.67)	34.25%
Overall (I–squared = 87.7%, p = 0.000)			1.23 (0.94, 1.60)	100.00%

Weights are from random effects analysis

0.8 1   2   3   4 5 6 7 8

Decreased risk   Increased risk

Supplementary Figure 8. Meta-analysis of risk ratios of primary open-angle glaucoma compared to no primary open-angle glaucoma on incident Alzheimer's disease

Abbreviations: CI, confidence interval