

REVIEW ARTICLE



Eye disease and mortality, cognition, disease, and modifiable risk factors: an umbrella review of meta-analyses of observational studies

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Globally, 2.2 billion people live with some form of vision impairment and/or eye disease. To date, most systematic reviews examining associations have focused on a single eye disease and there is no systematic evaluation of the relationships between eye diseases and diverse physical and mental health outcomes. Moreover, the strength and reliability of the literature is unclear. We performed an umbrella review of observational studies with meta analyses for any physical and/or mental comorbidities associated with eye disease. For each association, random-effects summary effect size, heterogeneity, small-study effect, excess significance bias and 95% prediction intervals were calculated, and used to grade significant evidence from convincing to weak. 34 studies were included covering 58 outcomes. No outcomes yielded convincing evidence, six outcomes yielded highly suggestive results (cataract positively associated with type 2 diabetes, open-angled glaucoma positively associated with myopia and diabetes, diabetic retinopathy positively associated with cardiovascular disease and cardiovascular mortality, and retinopathy of prematurity positively associated with chorioamnionitis), eight outcomes yielded suggestive results (diabetic retinopathy positively associated with all-cause mortality and depression, diabetic macular oedema positively associated with dyslipidaemia, cataract positively associated with gout, nuclear sclerosis positively associated with all-cause mortality, open angled glaucoma positively associated with migraine and hypertension, and age-related macular degeneration positively associated with diabetes), and 18 outcomes yielded weak evidence. Results show highly suggestive or suggestive evidence for associations between several types of eye diseases with several comorbid outcomes. Practitioners and public health policies should note these findings when developing healthcare policies.

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INTRODUCTION

Globally, it is estimated that ~2.2 billion people live with some form of vision impairment and/or eye disease, with at least 1 billion of these having preventable visual impairment [1, 2]. The leading causes of visual impairment include several eye diseases, including cataract, glaucoma, and diabetic retinopathy [3], with prevalence rates accelerating over the last 10 years due to population growth and ageing. There are also large differences in eye disease prevalence depending on geographic location, with the greatest prevalence being in low income countries [3].

A large body of literature reports that those with eye disease may be at a higher risk of physical and mental health complications when compared to those who are normally sighted (e.g. mobility limitations [4], chronic kidney disease [5], gout [6], obstructive sleep apnoea [7], depression [8], lower cognitive function [9], and suicidal behaviour [10]) and, importantly, increased risk of cardiovascular disease mortality [11, 12].

Given the incidence, morbidity, and mortality rates associated with eye disease, numerous systematic reviews and meta-analyses

have attempted to quantify this disparate literature. To date, most systematic reviews have focused on a single eye disease end point and there has not been a systematic evaluation of the relationships between eye disease and diverse physical and mental health outcomes. Moreover, the strength and reliability of the relationships reported in the literature is unclear. In order to address the breadth of the literature of complex conditions and comorbid outcomes, an increasing number of studies have used an 'umbrella review' approach (i.e., the syntheses of existing systematic reviews with meta-analyses, to capture the breadth of outcomes associated with a given exposure) [13, 14].

Therefore, the aim of the present study is to assess the strength and credibility of the evidence on eye disease and associated health outcomes derived from meta-analyses of observational studies using an umbrella review approach, aiming to the answer the following questions:

1. Which comorbid outcomes are associated with eye diseases?

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- What is the epidemiological credibility of the relationships between eye diseases and comorbid outcomes?

METHODS

An umbrella review was carried out following standardised procedures [13, 15]. The protocol for the present umbrella review was preregistered with PROSPERO (registration number CRD42018093358).

Search strategy and selection criteria

We searched PsycINFO, Medline, CINAHL, and Embase databases (from inception to 15/03/2021) to identify systematic reviews with meta-analyses, pooling observational (cross-sectional, case-control, cohort) studies to examine any association between eye disease and any comorbidity/medical condition. The following search key was used:

“(meta-analysis or meta-anal or systematic review) AND (vision OR visual* impair* OR eyesight OR blindness OR macular degeneration OR retinopathy OR cataract OR glaucoma OR corneal opacit* OR trachoma OR onchocerciasis)”*.

Two independent reviewers (MT, DP) searched titles/abstracts for eligibility, and then evaluated the full text of those articles surviving title/abstract phase. A third reviewer resolved any potential conflict (LS). When more than one meta-analysis assessed the same risk factor or the same outcome, we only included the one with the greatest number of included studies [16–18]. Exclusion criteria were: 1) meta-analyses of randomised controlled trials (RCTs); 2) studies published in languages other than English, 3) meta-analyses reporting only one study for an outcome, since no meta-analysis was possible.

Data extraction

Data was independently extracted by two investigators (MT, DP) into a pre-prepared spreadsheet. For each meta-analysis, we extracted PMID/DOI, first author, publication year, population included in the study, study design, number of included studies, the total sample size and number of cases, i.e. people having the outcome of interest. The methodological quality of each included meta-analysis was assessed with the Assessment of multiple systematic reviews (AMSTAR) 2 tool (available at <https://amstar.ca/Amstar-2.php>), which is a recent update of AMSTAR [19], by two independent investigators (MT, DP). The AMSTAR2 tool was chosen because it has been used in several similar umbrella reviews [20–22].

Data analysis

For each association of meta-analyses providing individual study data, we extracted effect sizes (ESs) of individual studies and re-performed the meta-analysis calculating the pooled effect size and the 95% confidence intervals (CIs), with random-effects models [23]. Heterogeneity was assessed with the I^2 statistic [24]. Additionally, we calculated the 95% prediction intervals (PIs) for the summary random ESs providing the possible range in which the ESs of future studies is expected to fall [25].

We also tested the presence of small-study effect bias [16, 26–28], which is deemed to be present in case of both pooled estimates larger than the individual largest study, and publication bias (Egger’s regression asymmetry test $p < 0.10$). We then assessed the existence of excess significance bias by evaluating whether the observed number of studies with nominally statistically significant results ($p < 0.05$) was different from the expected number of studies with statistically significant results (significance threshold set at $p < 0.10$) [28, 29], a test designed to assess whether the published meta-analyses comprise an over-representation of false positive findings [28].

Assessment of the credibility of the evidence

Credibility of meta-analyses providing individual study data was assessed according to stringent criteria based on previously published umbrella reviews [18, 20, 26, 27, 30, 31]. In brief, associations that presented nominally significant random-effects summary effect sizes ($p < 0.05$) were ranked as convincing, highly suggestive, suggestive, and weak evidence based on number of events, strength of the association, and the presence of several biases (criteria available in Supplementary Table 1).

RESULTS

Search

The flow diagram of search, selection and inclusion process is fully reported in Supplementary Fig. 1. Out of 9239 hits initially identified, after duplicate removal, 4508 were assessed at title/abstract level. Finally, 34 systematic reviews and meta-analyses were included examining a total of 58 independent outcomes [5–7, 32–62].

Findings from the case-control and cross-sectional studies

Overall, 41 outcomes were assessed by case-control or cross-sectional studies. The most common outcome examined was modifiable risk factors ($n = 14$), followed by mental health/cognition outcomes ($n = 12$), disease outcomes ($n = 11$), pregnancy related condition ($n = 2$), and visual impairment ($n = 2$). The median number of studies was 7 and the median number of participants was 3865. Full information can be found in Table 1 and Fig. 1.

The p value for effect-size, under a random effects model, was < 0.05 in 24/41 outcomes, and three reported a p value $< 1 \times 10^{-6}$. Among the 41 outcomes, 18 reported low heterogeneity ($I^2 < 50\%$), 11 moderate heterogeneity (I^2 between 50 and 75%) and 12 high heterogeneity. Small study effect affected 10/41 outcomes, whilst 6/41 had excess significance bias (see Table 1). The largest study, in terms of participants, for each outcome was significant in 19 associations. For five outcomes, the PIs excluded the null value.

Using the criteria to grade the quality of the evidence, no outcome reached a convincing evidence (class I), three outcomes reached highly suggestive evidence (class II), six reached suggestive evidence (class III), 15 a weak strength of evidence (class IV), and 17 outcomes had no statistical significance. Regarding the class II evidence, open-angle glaucoma was associated with a myopia ($n = 11$ studies; OR = 1.92; 95% CI: 1.54–2.38) and with diabetes ($n = 13$ studies; OR = 1.46; 95% CI: 1.27–1.68); and any cataract was associated with a higher presence of type 2 diabetes (OR = 1.64; 95% CI: 1.42–1.88) (see Table 1).

Findings from cohort studies

Overall, 17 outcomes were explored in prospective and retrospective designs. Mortality was the most explored outcome ($n = 9$), followed by pregnancy conditions ($n = 4$), disease outcomes ($n = 3$), and modifiable risk factors ($n = 1$). The median number of studies was 10, and the median number of participants was 30,118. Full information can be found in Table 2 and Fig. 1.

Almost half (8/17) of the associations included were statistically significant under a random-effects model, with three outcomes having a p value $< 1 \times 10^{-6}$. Among the 17 outcomes included, six were of low heterogeneity ($I^2 < 50\%$), three were of moderate heterogeneity (I^2 between 50 and 75%) and eight were of high heterogeneity. Small study effects were present in five outcomes, and three outcomes showed excess significance bias (see Table 2). The largest study, in terms of participants, for each outcome was significant in 10/17 outcomes.

Using the criteria to grade the quality of the evidence, no outcome reached a convincing evidence (class I), three reached highly suggestive evidence (class II), two reached suggestive evidence (class III) and three showed weak strength of evidence (class IV). Regarding class II evidence, retinopathy of prematurity

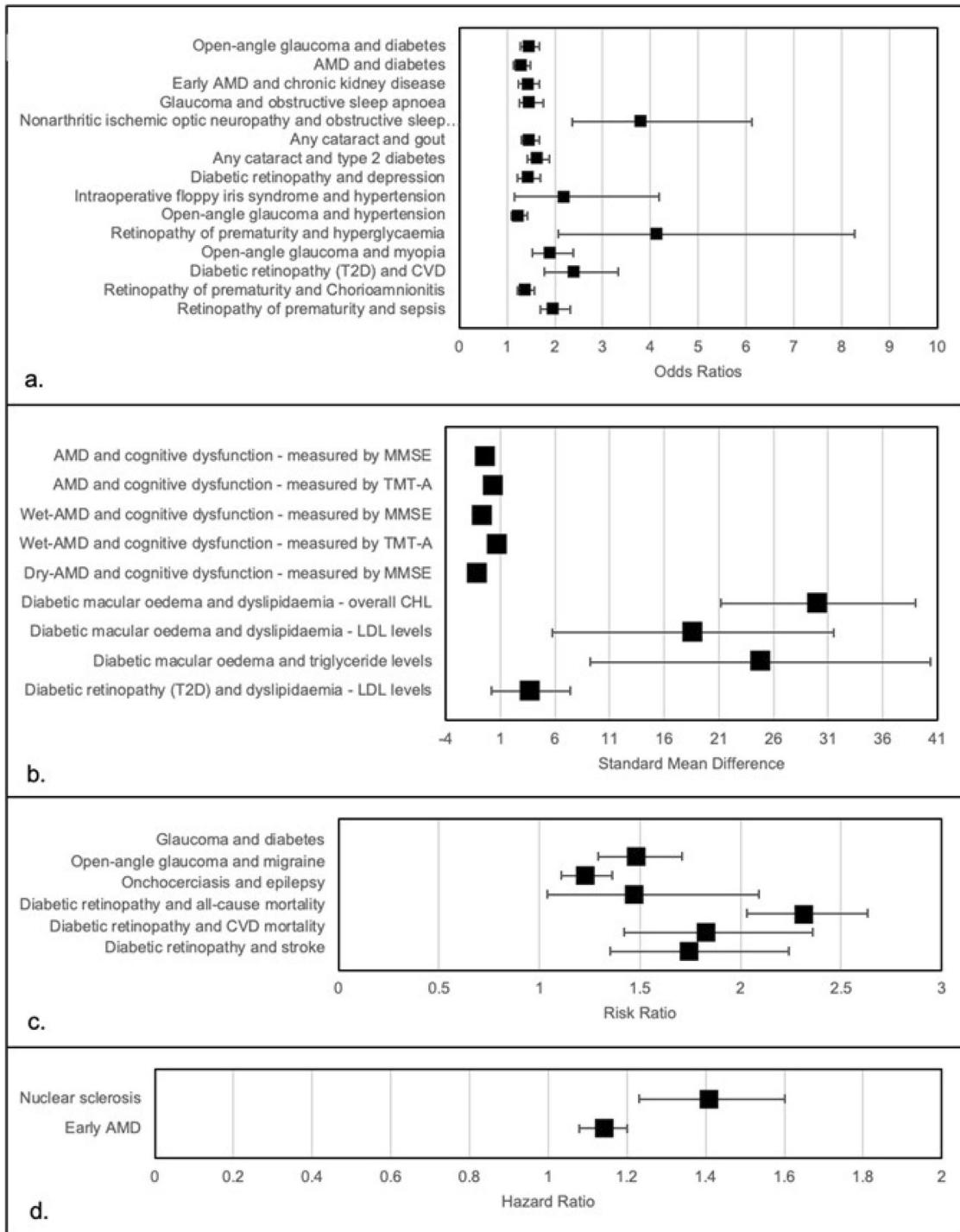


Fig. 1 Significant associations between various eye diseases and health outcomes. a odds ratios; **b** standard mean difference; **c** risk ratio; **d** hazard ratio.

was associated with a higher incidence of chorioamnionitis ($n = 71$ studies; OR = 1.38; 95% CI: 1.3–1.57) and a higher risk of sepsis ($n = 42$; OR = 1.98; 95% CI: 1.69–2.33), and diabetic retinopathy was positively associated with incident cardiovascular disease ($n = 12$; OR = 2.42; 95% CI: 1.77–3.32).

Study quality

The majority of meta-analyses scored critically low ($n = 31/34$) on AMSTAR2, and three scored low (see Table 3). The main reasons for the critically low scoring was that most studies failed to report

an explicit statement that the review methods were established prior to the conduct of the review (AMSTAR2 question 2; 3/34 studies satisfied this criteria) and failed to provide a list of excluded studies and justify the exclusions (AMSTAR2 question 7; 1/34 studies satisfied this criteria).

DISCUSSION

The present review, including 34 studies and 58 outcomes associated with varying eye diseases, no convincing (Class I)

Table 1. Main findings of the case-control and cross-sectional studies.

Visual impairment type	Outcome	Type of metric	No. of studies	Cases	Sample size	Effect size (95% CI)	P	I ²	Small study effect	Excess significance bias	Largest study significant	PI	Level of evidence
<i>Diseases</i>													
Open-angle glaucoma	Diabetes	OR	13	11,472	3,480,114	1.46 (1.27–1.68)	<0.001	70.8	No	Yes	Yes	0.76–1.67	II
	Chlamydia pneumoniae	OR	7	758	1395	1.11 (0.78–1.57)	0.570	40.3	No	No	No	–0.89–0.26	NS
AMD	Diabetes	OR	11	NA	175,305	1.30 (1.13–1.49)	<0.001	73.3	No	NA	Yes	–28.02–46.18	III
	Chronic kidney disease	OR	14	NA	299,374	1.44 (1.24–1.68)	<0.001	69.9	No	NA	Yes	NA	IV
Glaucoma	Diabetes	RR	29	NA	NA	1.48 (1.29–1.71)	<0.001	82.6	No	NA	NA	1.02–3.60	IV
	Obstructive sleep apnoea	OR	18	651,335	9,179,644	1.48 (1.26–1.75)	<0.001	83.8	Yes	Yes	No	0.81–2.70	IV
Nonarthritic ischemic optic neuropathy	OR	13	905	1332	3.8 (2.36–6.13)	<0.001	49.7	Yes	Yes	Yes	0.88–1.77	IV	
Any cataract	Gout	OR	20	NA	56,248	1.47 (1.29–1.68)	<0.001	0.0	Yes	NA	No	0.98–1.55	III
	Type 2 Diabetes	OR	23	NA	66,718	1.64 (1.42–1.88)	<0.001	60.9	Yes	NA	Yes	0.86–4.54	II
Diabetic retinopathy (T1D)	Metabolic syndrome	OR	13	NA	10,651	1.38 (0.99–1.91)	0.060	71.4	Yes	NA	No	–27.14–64.37	NS
	Non-alcoholic fatty liver disease	OR	9	NA	7170	0.94 (0.51–1.72)	0.810	96.3	Yes	NA	Yes	0.10–8.79	NS
<i>Mental health/cognition</i>													
Diabetic retinopathy	Depression	OR	20	4912	16,553	1.43 (1.21–1.69)	<0.001	81.8	Yes	Yes	Yes	1.15–2.63	III
	Migraine	RR	11	NA	467,008	1.23 (1.11–1.36)	<0.001	42.2	No	NA	Yes	0.44–4.27	III
AMD	Cognitive dysfunction - measured by MMSE	Standard mean difference	5	NA	1566	–0.32 (–0.51; –0.13)	0.001	51.6	No	NA	Yes	–12.22–19.76	IV
	Cognitive dysfunction - measured by TMT-A	Standard mean difference	2	NA	435	0.32 (0.13–0.51)	0.001	0.0	NA	No	Yes	–3.24–0.96	IV
Wet-AMD	Cognitive dysfunction - measured by TMT-B	Standard mean difference	2	NA	435	0.10 (–0.10–0.29)	0.330	0.0	NA	No	No	–1.85–0.69	NS
	Cognitive dysfunction - measured by MMSE	Standard mean difference	3	NA	543	–0.58 (–0.78; –0.38)	<0.001	0.0	No	NA	Yes	0.51–33.81	IV
Dry-AMD	Cognitive dysfunction - measured by TMT-A	Standard mean difference	2	NA	435	0.76 (0.13–1.39)	0.020	78.5	NA	No	Yes	0.53–1.50	IV
	Cognitive dysfunction - measured by TMT-B	Standard mean difference	2	NA	435	0.32 (–0.04–0.69)	0.080	44.9	NA	No	Yes	0.94–2.85	NS
Onchocerciasis	Cognitive dysfunction - measured by MMSE	Standard mean difference	3	NA	543	–1.16 (–1.72; –0.60)	<0.001	44.2	No	NA	No	0.53–3.52	IV
	Cognitive dysfunction - measured by TMT-A	Standard mean difference	2	NA	435	1.22 (–0.18–2.62)	0.090	91.8	NA	NA	Yes	0.72–1.87	NS
Modifiable risk factors	Cognitive dysfunction - measured by TMT-B	Standard mean difference	2	NA	435	0.22 (–0.16–0.61)	0.250	0.0	NA	NA	No	NA	NS
	Epilepsy	RR	9	NA	5293	1.47 (1.04–2.09)	0.030	81.0	Yes	NA	No	0.90–1.08	IV
<i>Modifiable risk factors</i>													
7 NA 1125 <0.001 99.7 No NA Yes 0.66–2.80 III													

Table 1 continued

Visual impairment type	Outcome	Type of metric	No. of studies	Cases	Sample size	Effect size (95% CI)	P	I ²	Small study effect	Excess significance bias	Largest study significant	PI	Level of evidence
Diabetic Macular Oedema	Dyslipidaemia - overall CHL	Standard mean difference	7	NA	1125	30.08 (21.15–39.02)	0.008	99.9	No	NA	No	0.79–7.41	IV
	Dyslipidaemia - LDL levels	Standard mean difference	7	NA	1125	18.62 (5.73–31.51)	0.008	99.9	No	NA	No	0.79–7.41	IV
	Triglyceride levels	Standard mean difference	7	NA	1125	24.82 (9.21–40.42)	0.002	99.8	No	NA	No	0.77–2.64	IV
Diabetic retinopathy (T2D)	Dyslipidaemia - LDL levels	Standard mean difference	7	NA	1125	2.24 (-0.18–4.67)	0.070	99.9	No	NA	No	0.18–59.90	NS
	Dyslipidaemia - overall CHL levels	Mean difference	4	NA	3465	3.74 (0.13–7.35)	0.040	19.7	No	NA	No	-23.18–72.80	IV
	Dyslipidaemia - HDL levels	Mean difference	6	NA	4032	3.77 (-2.45–9.99)	0.240	41.0	No	NA	No	-8.71–4.43	NS
Diabetic retinopathy (T2D)	Dyslipidaemia - overall CHL levels	Mean difference	5	NA	3698	-1.14 (-2.43–0.15)	0.080	0.0	No	NA	No	0.81–2.44	NS
	Dyslipidaemia - HDL levels	Mean difference	7	NA	4366	9.08 (-4.20–22.36)	0.180	64.6	No	NA	No	0.71–1.96	NS
	Triglyceride levels	Mean difference	6	NA	7408	1.37 (0.96–1.95)	0.080	45.5	No	NA	No	1.28–1.70	NS
Diabetic Retinopathy	Blood pressure	OR	6	NA	23,830	0.89 (0.75–1.07)	0.210	65.5	No	NA	No	NA	NS
	BMI - overweight	OR	6	NA	23,830	0.97 (0.73–1.30)	0.860	72.6	No	NA	No	0.47–1.64	NS
	BMI - obese	OR	2	NA	1399	2.2 (1.15–4.19)	0.020	0	NA	NA	Yes	0.41–2.30	IV
Intraoperative floppy iris syndrome	Hypertension	OR	4	NA	3281	1.26 (0.71–2.21)	0.430	0.0	No	NA	No	NA	NS
	Diabetes	OR	17	NA	60,084	1.25 (1.09–1.43)	0.001	29.3	No	NA	No	-6.94–14.42	III
Open-angle glaucoma	Hypertension	OR	17	NA	60,084	1.25 (1.09–1.43)	0.001	29.3	No	NA	No	-6.94–14.42	III
	Blood pressure	OR	6	NA	7408	1.37 (0.96–1.95)	0.080	45.5	No	NA	No	1.28–1.70	NS
	BMI - overweight	OR	6	NA	23,830	0.89 (0.75–1.07)	0.210	65.5	No	NA	No	NA	NS
Pregnancy related conditions	BMI - obese	OR	2	NA	1399	2.2 (1.15–4.19)	0.020	0	NA	NA	Yes	0.41–2.30	IV
	Diabetes	OR	4	NA	3281	1.26 (0.71–2.21)	0.430	0.0	No	NA	No	NA	NS
Retinopathy of prematurity	Hypertension	OR	4	NA	3281	1.26 (0.71–2.21)	0.430	0.0	No	NA	No	NA	NS
	Diabetes	OR	17	NA	60,084	1.25 (1.09–1.43)	0.001	29.3	No	NA	No	-6.94–14.42	III
Visual impairment	Myopia	OR	11	NA	43,958	1.92 (1.54–2.38)	<0.001	53.0	Yes	NA	Yes	0.32–5.64	II
	Open-angle glaucoma	OR	7	NA	27,638	0.83 (0.66–1.04)	0.100	36.7	No	NA	No	1.08–1.20	NS
Diabetic retinopathy	Myopia	OR	7	NA	27,638	0.83 (0.66–1.04)	0.100	36.7	No	NA	No	1.08–1.20	NS
	Open-angle glaucoma	OR	11	NA	43,958	1.92 (1.54–2.38)	<0.001	53.0	Yes	NA	Yes	0.32–5.64	II

PI prediction interval, AMD advanced macular degeneration, T2D Type 2 diabetes, T1D Type 1 diabetes, CHL cholesterol, LDL low-density lipoprotein, HDL high-density lipoprotein, BMI Body mass index, MMSE mini-mental state examination, TMT-A Trial making test part A, TMT-B Trial making test part B, OR Odds ratio, RR Risk ratio, NS Non-significant.

Table 2. Main findings of the prospective and retrospective studies.

Visual impairment type	Outcome/Type of comorbidity	Type of metric	No. of studies	Cases	Sample size	Effect size (95% CI)	P	I ²	Small study effects	Excess significance bias	Largest study significant	PI	Level of evidence
<i>Mortality</i>													
Nuclear sclerosis	All-cause mortality	HR	23	13,463	86,160	1.41 (1.23–1.60)	<0.001	78.2	Yes	NA	No	0.52–4.2	III
Diabetic retinopathy	All-cause mortality	RR	38	NA	29,647	2.31 (2.03–2.63)	<0.001	68.2	Yes	NA	No	5.69–169.00	III
Diabetic retinopathy (T2D)	CVD mortality	RR	10	NA	11,239	1.83 (1.42–2.36)	<0.001	76.3	No	NA	No	0.81–4.13	IV
Diabetic retinopathy (T2D)	CVD	OR	12	NA	16,787	2.42 (1.77–3.32)	<0.001	81.2	Yes	NA	Yes	0.99–2.16	II
Early AMD	All-cause mortality	HR	26	3294	12,284	1.14 (1.08–1.20)	<0.001	0.0	No	NA	No	0.93–15.44	IV
AMD	Cancer mortality	HR	6	1024	20,329	1.07 (0.86–1.34)	0.55	37.9	No	No	Yes	NA	NS
AMD	CVD mortality	HR	11	NA	NA	1.16 (0.97–1.39)	0.10	42.3	No	NA	NA	0.61–1.88	NS
AMD	CVD mortality	RR	5	NA	17,250	1.18 (0.98–1.43)	0.09	33.6	No	NA	Yes	0.41–2.86	NS
Open-angle glaucoma	All-cause mortality	RR	9	NA	2,636	1.13 (0.97–1.31)	0.12	50.6	No	NA	NA	0.72–2.00	NS
<i>Diseases</i>													
Diabetic retinopathy	Stroke	RR	5	NA	7,727	1.74 (1.35–2.24)	<0.001	0.0	No	NA	Yes	0.47–1.44	IV
AMD	Diabetes	RR	5	NA	139,200	1.06 (0.99–1.13)	0.10	5.3	No	NA	Yes	0.94–1.78	NS
AMD	Stroke	OR	9	NA	1,420,978	1.08 (0.81–1.43)	0.59	96	No	NA	Yes	0.9–2.31	NS
<i>Pregnancy related conditions</i>													
Retinopathy of prematurity	Chorioamnionitis	OR	71	NA	49,710	1.38 (1.21–1.57)	<0.001	62.5	Yes	NA	Yes	0.36–4.35	II
Retinopathy of prematurity	Sepsis	OR	42	16,286	79,408	1.98 (1.69–2.33)	<0.001	80.4	Yes	Yes	Yes	0.99–1.65	II
Retinopathy of prematurity	Gestational hypertensive disorder	OR	7	4356	32,890	1.35 (0.88–2.08)	0.17	83.8	No	Yes	Yes	0.93–1.20	NS
Retinopathy of prematurity	Pre-eclampsia	OR	7	4356	32,890	1.29 (0.81–2.05)	0.28	84.5	No	Yes	Yes	NA	NS
<i>Modifiable risk factors</i>													
Diabetic retinopathy	BMI (as a continuous variable)	OR	23	NA	30,588	0.99 (0.97–1.00)	0.22	78.5	No	NA	No	NA	NS

PI prediction interval, AMD advanced macular degeneration, T2D Type 2 diabetes, BMI Body mass index, CVD Cardio-vascular disease, OR Odds ratio, RR Risk ratio, HR Hazard ratio, NS Non-significant.

Table 3. AMSTAR2 results.

Author of meta-analysis	Year of meta-analysis	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	AMSTAR 2 rating
Alkbari et al.	2009	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Marcus et al.	2011	Yes	No	Yes	Partial Yes	Yes	No	No	Partial Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Critically low
Li et al.	2014	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Zhou et al.	2014	Yes	No	Yes	Partial Yes	NO	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Chen et al.	2014	Yes	No	Yes	Partial Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Critically low
Bae et al.	2014	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	No	No	Yes	Yes	No	No	Yes	Yes	Critically low
Zhau et al.	2015	Yes	Yes	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Song et al.	2014	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Critically low
Shi et al.	2016	Yes	No	Yes	No	Yes	No	No	Partial Yes	Yes	No	Yes	No	No	Yes	Yes	No	Critically low
Au et al.	2015	Yes	No	Yes	Partial Yes	No	No	No	Partial Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Das et al.	2015	Yes	Yes	Yes	Partial Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Fernandez et al.	2015	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	No	No	Yes	No	No	Yes	No	Yes	Critically low
Zhou et al.	2016	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	No	No	Yes	No	No	No	No	Yes	Critically low
Chan et al.	2016	Yes	No	Yes	Partial Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Wang et al.	2016	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Critically low
Zhu et al.	2017	Yes	No	Yes	Partial Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	No	Yes	No	Critically low
McGuinness et al.	2017	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Critically low
Zhou et al.	2017	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Yes	No	Yes	No	No	No	Yes	Yes	Critically low
Luo et al.	2017	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Xu et al.	2018	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Critically low
Zhou et al.	2018	Yes	No	Yes	Partial Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No	No	Yes	Critically low
Zhou et al.	2018	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Yes	No	Yes	No	No	No	No	Yes	Critically low
Villamor-Martinez	2018	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Critically low
Chen et al.	2018	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Partial Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Huang et al.	2019	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Huon et al.	2016	Yes	No	Yes	Partial Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No	No	No	Yes	Critically low
Druet-Cabanac et al.	2004	Yes	No	Yes	No	Yes	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	Critically low
Wu and You	2018	Yes	No	Yes	Partial Yes	Yes	Yes	No	No	NO	No	No	No	No	Yes	Yes	No	Critically low
Xin et al.	2018	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	No	Critically low
Wang et al.	2016	Yes	No	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Guo et al.	2016	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Chatziralli and Sergentanis	2011	Yes	No	Yes	No	Yes	Yes	No	No	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Song et al.	2020	Yes	No	Yes	Partial yes	Yes	Yes	No	Partial yes	Yes	No	Yes	No	No	No	Yes	Yes	Critically low
Xu et al.	2020	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Low

AMSTAR@ Questions: Q1: Did the research questions and inclusion criteria for the review include the components of PICO?; Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?; Q3: Did the review authors explain their selection of the study designs for inclusion in the review?; Q4: Did the review authors use a comprehensive literature search strategy?; Q5: Did the review authors perform study selection in duplicate?; Q6: Did the review authors perform data extraction in duplicate?; Q7: Did the review authors provide a list of excluded studies and justify the exclusions?; Q8: Did the review authors describe the included studies in adequate detail?; Q9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?; Q10: Did the review authors report on the sources of funding for the studies included in the review?; Q11: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?; Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?; Q13: Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?; Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?; Q15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?; Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?.

evidence for any comorbidity across all eye diseases was found. Highly suggestive levels of evidence (Class II) for cohort, case-control and cross-sectional studies showed that people with diabetic retinopathy were nearly 2.5 times more likely to suffer from cardiovascular diseases, and 1.8 times more likely to suffer CVD mortality. Diabetic retinopathy is a microvascular disease and it is not surprising that cardiovascular diseases will have a significant effect on the eye, with sepsis and chorioamnionitis being significant risk factors for retinopathy of prematurity [63]. Furthermore, babies with retinopathy of prematurity are nearly twice as likely to suffer from sepsis [53]. Retinopathy of prematurity is a vasoproliferative disease that affects the retinal vascular system in premature babies. As infection is a significant risk factor for neonatal brain damage, and sepsis is the key cause of neonatal inflammation, this could be the reason why the strong association with retinopathy of prematurity has been found. The foetal inflammatory response induced by chorioamnionitis [64], leads to proinflammatory cytokines having a substantial effect on retinal angiogenesis and subsequent development of the retina [65, 66], which could lead to retinopathy of prematurity.

Our analysis shows people suffering from open angle glaucoma are twice as likely to suffer from diabetes. Diabetes is a serious condition and its effects on macrovascular and micro vascular structures are well documented [67, 68]. While the strong association of diabetes and cataract is well known, the link with open angle glaucoma has been open to debate. Our analysis shows highly suggestive evidence of the link between diabetes and open angle glaucoma. One possible mechanism could be because long standing hyperglycaemia increases the risk of neural injury and the reduced capacity for auto-regulation of blood in diabetes could have an effect on the optic nerve and nerves in the eye. Furthermore, diabetes affects nerves in the body (neuropathy) and research has shown diabetes having a negative effect on ganglion cells in the eye [69].

Myopia also yielded a highly suggestive (Class II) association with open angle glaucoma. One possible mechanism is the biomechanical stress induced by increased axial length and oxidative stress, although this needs further investigation. The increasing global prevalence of myopia would have significant consequences on the global burden of eye diseases beyond just refractive error, and may explain, to a certain extent, the increasing prevalence of open angle glaucoma worldwide.

Suggestive levels of evidence (Class III) include cataract (including nuclear sclerosis) being associated with all-cause mortality and gout, diabetic retinopathy with depression, and open angle glaucoma with hypertension and migraine. Weaker strength of evidence (Class IV) links AMD with cognitive function, and glaucoma with sleep apnoea. Further studies need to be carried out to strengthen and confirm possible association between these conditions and the eye diseases.

Umbrella reviews provide top-tier evidence and important insights, however there are a number of limitations. Although we measured for heterogeneity, the meta-analyses included in this study included differing study designs, methods of measuring VI and eye diseases and populations. Furthermore, meta-analyses have inherent limitations [70]: their findings are dependent on estimates that are selected from each primary study and how they are applied in the meta-analysis. Finally, almost all of the studies included scored 'critically low' in quality control. Some studies were scored low as they had missed quality indicators such as confirming review methods or details about excluded studies. It is important that all the quality indicators are included in order to assure confidence in the data presented.

CONCLUSION

Our results show highly suggestive evidence for associations between diabetic retinopathy and cardiovascular disease,

open angle glaucoma and diabetes, myopia and open angle glaucoma. Furthermore, we found suggestive evidence for associations between cataract and all-cause mortality and gout, depression and diabetic retinopathy, and hypertension and migraine for open angle glaucoma. Clinicians should take note of these and consider these associations in the delivery of care. Furthermore, public health policies should reflect and accommodate these associations in healthcare policies, practices and guidelines.

Summary table

What this study adds

- This is the first study to examine the credibility of evidence against strict statistical criteria of eye disease and all types of health outcomes.
- Six significant associations were classified as 'highly suggestive', including cataract and type 2 diabetes; open-angled glaucoma, myopia and diabetes; diabetic retinopathy, cardiovascular disease, and cardiovascular mortality; and retinopathy of prematurity and chorioamnionitis.
- Eight significant associations were classified as 'suggestive', including diabetic retinopathy, all-cause mortality, and depression; diabetic macular oedema and dyslipidaemia; cataract and gout; nuclear sclerosis and all-cause mortality; open angled glaucoma, migraine, and hypertension; age-related macular degeneration and diabetes.
- 18 significant associations were classified as 'weak'.

Study limitations

- The risk of bias of included meta-analyses was high.
- This study included only meta-analyses of observation studies, which carry inherent limitations.

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AUTHOR CONTRIBUTIONS

MT: conceptualisation, data collection, writing manuscript. LS: conceptualisation, supervision, critical appraisal of manuscript and revision writing; NV: conceptualisation, data analysis, writing manuscript, revision of manuscript; DP: conceptualisation, data analysis, writing manuscript, revision of manuscript; YB: conceptualisation, writing manuscript, critical appraisal; TG: conceptualisation, writing manuscript,

critical appraisal; SP: conceptualisation, supervision, critical appraisal of manuscript and revision writing.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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