Eye Disease and Mortality, Cognition, Disease, and Modifiable Risk Factors: An Umbrella Review of Meta-analyses of Observational Studies

Mike Trott1\*, Lee Smith1, Nicola Veronese2,3, Damiano Pizzol4, Yvonne Barnett5, Trish Gorely6, Shahina Pardhan7

1 - The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK; 2 - National Research Council, Neuroscience Institute, Aging Branch, Padua, Italy; 3 – University of Palermo, Department of Geriatrics, Palermo, Italy; 4 -Italian Agency for Development Cooperation (Khartoum), Sudan; 5- School of Life Sciences, Anglia Ruskin University, Cambridge, UK; 6 – Department of Nursing and Midwifery, University of the Highlands and Islands, Centre for Health Sciences, Old Perth Road, Inverness, IV2 3JH, UK; 7 - Vision and Eye Research Institute (VERI), School of Medicine, Anglia Ruskin University, East Road, Cambridge, CB1 1PT

\*Corresponding Author

Mike Trott; The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge UK, CB1 1PT; [mt472@pgr.anglia.ac.uk](mailto:mt472@pgr.anglia.ac.uk)

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# Abstract

**Importance**: 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.

**Objective**: 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.

**Findings**: 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.

**Conclusions**: 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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| **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. |

# Introduction

Globally, it is estimated that approximately 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 impairment1,2. The leading causes of visual impairment include several eye diseases, including cataract, glaucoma, and diabetic retinopathy3, 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 countries3.

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 limitations4, chronic kidney disease5, gout6, obstructive sleep apnoea7, depression8, lower cognitive function9, and suicidal behaviour10) and, importantly, increased risk of cardiovascular disease mortality11,12.

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

# Methods

An umbrella review was carried out following standardized procedures13,15. The protocol for the present umbrella review was preregistered with PROSPERO (registration number CRD42018093358).

## 2.1 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 studies16–18. Exclusion criteria were: 1) meta-analyses of randomized 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.

## 2.2 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 AMSTAR19, by two independent investigators (MT, DP). The AMSTAR2 tool was chosen because it has been used in several similar umbrella reviews20–22.

## 2.3 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 models23. Heterogeneity was assessed with the I2 statistic24. 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 fall25.

We also tested the presence of small-study effect bias16,26–28, 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 findings28*.*

## 2.4 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 reviews18,20,26,27,30,31. 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

## 3.1 Search

The flow diagram of search, selection and inclusion process is fully reported in **Supplementary** **Figure 1**. Out of 9,239 hits initially identified, after duplicate removal, 4,508 were assessed at title/abstract level. Finally, 34 systematic reviews and meta-analyses were included examining a total of 58 independent outcomes5–7,32–62.

## 3.2 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 3,865. Full information can be found in **Table 1 and** **Figure 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\*10-6. Among the 41 outcomes, 18 reported low heterogeneity (I2<50%), 11 moderate heterogeneity (I2 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**).

## 3.3 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 Figure 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\*10-6. Among the 17 outcomes included, six were of low heterogeneity (I2<50%), three were of moderate heterogeneity (I2 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 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).

## 3.4 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) 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 prematurity63. Furthermore, babies with retinopathy of prematurity are nearly twice as likely to suffer from sepsis53. 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 chorioamnionitis64, leads to proinflammatory cytokines having a substantial effect on retinal angiogenesis and subsequent development of the retina65,66, 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 documented67,68. 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 eye69.

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 limitations70: 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.

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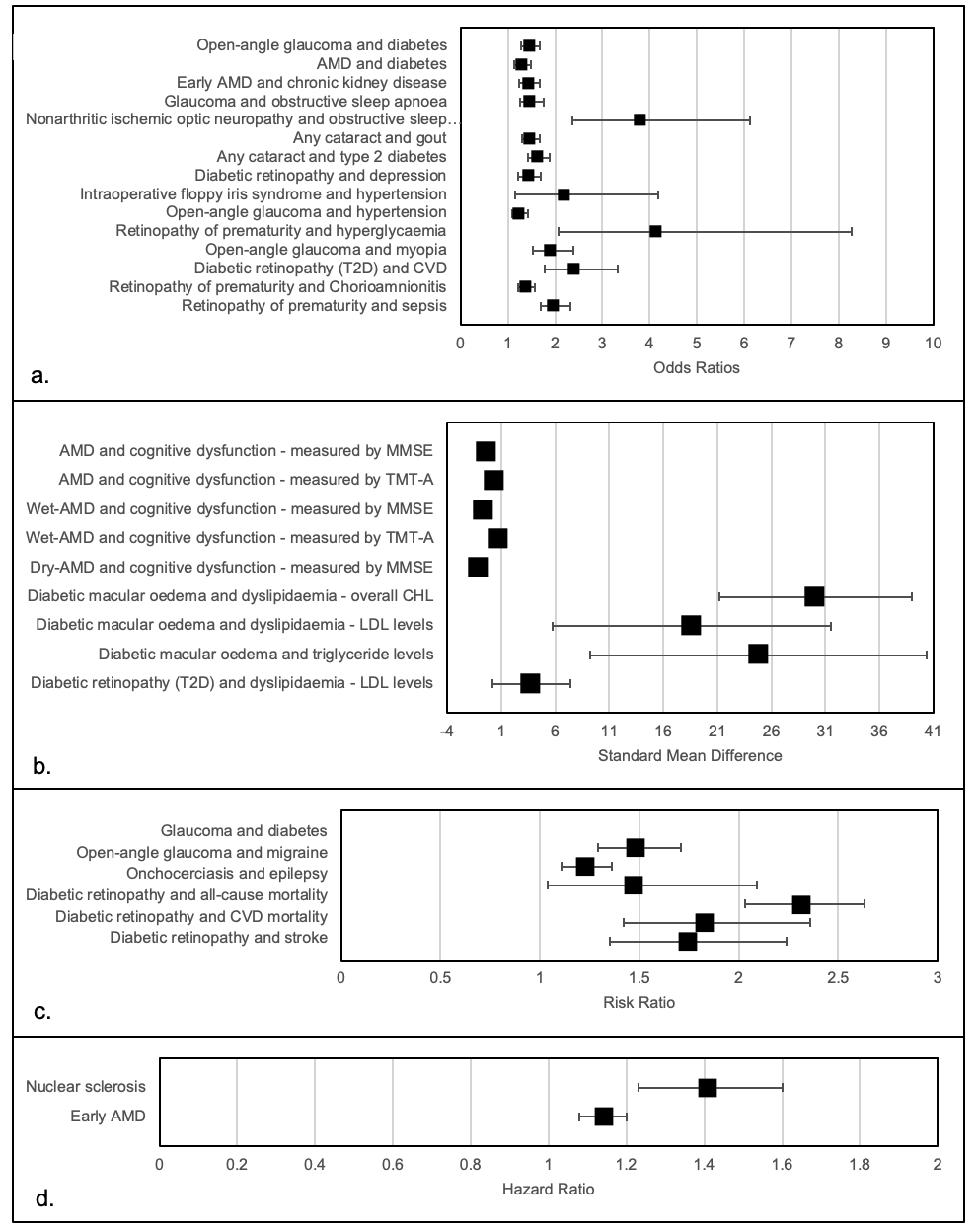
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# Tables and Figures

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

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

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Visual impairment type | Outcome | Type of metric | N of studies | Cases | Sample size | Effect size  (95% CI) | P | I2 | Small study effect | Excess significance bias | Largest study significant | PI | Level of evidence | |
| *Diseases* | | | | | | | | | | | | | |
| 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 |
| AMD | Chlamydia pneumoniae | OR | 7 | 758 | 1,395 | 1.11  (0.78-1.57) | 0.570 | 40.3 | no | no | no | -0.89-0.26 | NS |
| Diabetes | OR | 11 | NA | 175,305 | 1.30  (1.13-1.49) | <0.001 | 73.3 | no | NA | yes | -28.02-46.18 | III |
| Early AMD | 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 | Obstructive sleep apnoea | OR | 13 | 905 | 1,332 | 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 |
| Diabetic retinopathy | Non-alcoholic fatty liver disease | OR | 9 | NA | 7,170 | 0.94  (0.51-1.72) | 0.810 | 96.3 | yes | NA | Yes | 0.10-8.79 | NS |
| *Mental health/cognition* | | | | | | | | | | | | | |
| Diabetic retinopathy | Depression | OR | 20 | 4,912 | 16,553 | 1.43  (1.21-1.69) | <0.001 | 81.8 | yes | yes | yes | 1.15-2.63 | III |
| Open-angle glaucoma | 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 | 1,566 | -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 |
| 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 |
| Wet-AMD | 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 |
| 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 |
| Dry-AMD | 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 |
| 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 |
| Onchocerciasis | Epilepsy | RR | 9 | NA | 5,293 | 1.47  (1.04-2.09) | 0.030 | 81.0 | yes | NA | no | 0.90-1.08 | IV |
| *Modifiable risk factors* | | | | | | | | | | | | | |
| Diabetic Macular Oedema | Dyslipidaemia - overall CHL | Standard mean difference | 7 | NA | 1125 | 30.08  (21.15-39.02) | <0.001 | 99.7 | no | NA | yes | 0.66-2.80 | III |
| Dyslipidaemia - LDL levels | Standard mean difference | 7 | NA | 1,125 | 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 | 1,125 | 24.82  (9.21-40.42) | 0.002 | 99.8 | no | NA | no | 0.77-2.64 | IV |
| Dyslipidaemia - HDL levels | Standard mean difference | 7 | NA | 1,125 | 2.24  (-0.18-4.67) | 0.070 | 99.9 | no | NA | no | 0.18-59.90 | NS |
| Diabetic retinopathy (T2D) | Dyslipidaemia - LDL levels | Mean difference | 4 | NA | 3,465 | 3.74  (0.13-7.35) | 0.040 | 19.7 | no | NA | no | -23.18-72.80 | IV |
| Dyslipidaemia - overall CHL levels | Mean difference | 6 | NA | 4,032 | 3.77  (-2.45-9.99) | 0.240 | 41.0 | no | NA | no | -8.71-4.43 | NS |
| Dyslipidaemia - HDL levels | Mean difference | 5 | NA | 3,698 | -1.14  (-2.43-0.15) | 0.080 | 0.0 | no | NA | no | 0.81-2.44 | NS |
| Triglyceride levels | Mean difference | 7 | NA | 4,366 | 9.08  (-4.20-22.36) | 0.180 | 64.6 | no | NA | no | 0.71-1.96 | NS |
| Blood pressure | OR | 6 | NA | 7,408 | 1.37  (0.96-1.95) | 0.080 | 45.5 | no | NA | no | 1.28-1.70 | NS |
| Diabetic Retinopathy | BMI - overweight | OR | 6 | NA | 23,830 | 0.89  (0.75-1.07) | 0.210 | 65.5 | no | NA | no | NA | NS |
| BMI - obese | OR | 6 | NA | 23,830 | 0.97  (0.73-1.30) | 0.860 | 72.6 | no | NA | no | 0.47-1.64 | NS |
| Intraoperative floppy iris syndrome | Hypertension | OR | 2 | NA | 1,399 | 2.2  (1.15-4.19) | 0.020 | 0 | NA | NA | yes | 0.41-2.30 | IV |
| Diabetes | OR | 4 | NA | 3,281 | 1.26  (0.71-2.21) | 0.430 | 0.0 | no | NA | no | NA | NS |
| 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 |
| *Pregnancy related conditions* | | | | | | | | | | | | | |
| Retinopathy of prematurity | Hyperglycaemia | OR | 7 | 323 | 1,211 | 4.15  (2.08-8.28) | <0.001 | 65.4 | yes | yes | yes | 1.28-4.15 | IV |
| Pre-eclampsia | OR | 7 | 4,356 | 32,890 | 1.29  (0.81-2.05) | 0.280 | 84.5 | no | yes | yes | NA | NS |
| *Visual impairment* | | | | | | | | | | | | | |
| Open-angle glaucoma | Myopia | OR | 11 | NA | 43,958 | 1.92  (1.54-2.38) | <0.001 | 53.0 | yes | NA | yes | 0.32-5.64 | II |
| 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 |

Abbreviations: 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 | N of studies | Cases | Sample size | Effect size  (95% CI) | P | I2 | Small study effects | Excess significance bias | Largest study significant | PI | Level of evidence |
| *Mortality* | | | | | | | | | | | | | |
| 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 |
| 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 | 3,294 | 12,284 | 1.14  (1.08-1.20) | <0.001 | 0.0 | no | NA | no | 0.93-15.44 | IV |
| Cancer mortality | HR | 6 | 1,024 | 20,329 | 1.07  (0.86-1.34) | 0.55 | 37.9 | no | no | yes | NA | NS |
| 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 |
| *Diseases* | | | | | | | | | | | | | |
| 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 |
| Stroke | OR | 9 | NA | 1,420,978 | 1.08  (0.81-1.43) | 0.59 | 96 | no | NA | yes | 0.9-2.31 | NS |
| *Pregnancy related conditions* | | | | | | | | | | | | | |
| 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 | 4,356 | 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 | 4,356 | 32,890 | 1.29  (0.81-2.05) | 0.28 | 84.5 | no | yes | yes | NA | NS |
| *Modifiable risk factors* | | | | | | | | | | | | | |
| 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 |

Abbreviations: 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 |
| Akbari 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 | No | 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?