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

Mike Trott[1*], Lee Smith[1], Nicola Veronese[2,3], Damiano Pizzol[4], Yvonne Barnett[5], Trish Gorely[6], Shahina Pardhan[7]

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

Word count: 2,126

Financial Support: None

Declaration of interest: None

Running head: Eye disease and comorbidities: an umbrella review

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.

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.

1. 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 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?
2. What is the epidemiological credibility of the relationships between eye diseases and comorbid outcomes?

2. Methods

An umbrella review was carried out following standardized procedures[13,15]. 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 studies[16–18]. 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,

111 population included in the study, study design, number of included studies, the total sample
112 size and number of cases, i.e. people having the outcome of interest. The methodological
113 quality of each included meta-analysis was assessed with the Assessment of multiple
114 systematic reviews (AMSTAR) 2 tool (available at https://amstar.ca/Amstar-2.php), which is
115 a recent update of AMSTAR[19], by two independent investigators (MT, DP). The AMSTAR2
116 tool was chosen because it has been used in several similar umbrella reviews[20–22].
117
118 **2.3 Data analysis**
119 For each association of meta-analyses providing individual study data, we extracted effect
120 sizes (ESs) of individual studies and re-performed the meta-analysis calculating the pooled
121 effect size and the 95% confidence intervals (CIs), with random-effects models[23].
122 Heterogeneity was assessed with the I^2 statistic[24]. Additionally, we calculated the 95%
123 prediction intervals (PIs) for the summary random ESs providing the possible range in which
124 the ESs of future studies is expected to fall[25].
125
126 We also tested the presence of small-study effect bias[16,26–28], which is deemed to be present
127 in case of both pooled estimates larger than the individual largest study, and publication bias
128 (Egger's regression asymmetry test $p<0.10$). We then assessed the existence of excess
129 significance bias by evaluating whether the observed number of studies with nominally
130 statistically significant results ($p<0.05$) was different from the expected number of studies
131 with statistically significant results (significance threshold set at $p<0.10$)[28,29], a test designed
132 to assess whether the published meta-analyses comprise an over-representation of false
133 positive findings[28].
134

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 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**).

3. 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 outcomes[5–7,32–62].

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 (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**).

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 ($I^2<50\%$), 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 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).

4. 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 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

254 in the meta-analysis. Finally, almost all of the studies included scored ‘critically low’ in quality
255 control. Some studies were scored low as they had missed quality indicators such as
256 confirming review methods or details about excluded studies. It is important that all the
257 quality indicators are included in order to assure confidence in the data presented.

258

259

5. 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.

6. References

1. World Health Organization. Blindness and vision impairment: The key facts. 2019. Available at: https://www.who.int/en/news-room/fact-sheets/detail/blindness-and-visual-impairment [Accessed May 6, 2020].

2. Bourne RR, Flaxman SR, Braithwaite T, Cicinelli MV, Das A, Jonas JB, et al. Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis. Lancet Glob. Health. 2017; 5(9): e888–e897.

3. Fricke TR, Tahhan N, Resnikoff S, Papas E, Burnett A, Ho SM, et al. Global prevalence of presbyopia and vision impairment from uncorrected presbyopia: systematic review, meta-analysis, and modelling. Ophthalmology. 2018; 125(10): 1492–1499.

4. Swenor BK, Simonsick EM, Ferrucci L, Newman AB, Rubin S, Wilson V, et al. Visual impairment and incident mobility limitations: the health, aging and body composition study. J. Am. Geriatr. Soc. 2015; 63(1): 46–54.

5. Chen Y-J, Yeung L, Sun C-C, Huang C-C, Chen K-S, Lu Y-H. Age-Related Macular Degeneration in Chronic Kidney Disease: A Meta-Analysis of Observational Studies. Am. J. Nephrol. 2018; 48(4): 278–291.

6. Luo C, Chen X, Jin H, Yao K. The association between gout and cataract risk: A meta-analysis. PloS One. 2017; 12(6): e0180188.

7. Shi Y, Liu P, Guan J, Lu Y, Su K. Association between glaucoma and obstructive sleep apnea syndrome: a meta-analysis and systematic review. PloS One. 2015; 10(2): e0115625–e0115625.

8. Choi HG, Lee MJ, Lee S-M. Visual impairment and risk of depression: A longitudinal follow-up study using a national sample cohort. Sci. Rep. 2018; 8(1): 2083.

9. Hong T, Mitchell P, Burlutsky G, Liew G, Wang JJ. Visual impairment, hearing loss and cognitive function in an older population: longitudinal findings from the Blue Mountains Eye Study. PLoS One. 2016; 11(1).

10. Meyer-Rochow VB, Hakko H, Ojamo M, Uusitalo H, Timonen M. Suicides in Visually Impaired Persons: A Nation-Wide Register-Linked Study from Finland Based on Thirty Years of Data. PloS One. 2015; 10(10): e0141583–e0141583.

11. Rajala U, Pajunpää H, Koskela P, Keinänen-Kiukaanniemi S. High cardiovascular disease mortality in subjects with visual impairment caused by diabetic retinopathy. Diabetes Care. 2000; 23(7): 957.

12. McCarty CA, Nanjan MB, Taylor HR. Vision impairment predicts 5 year mortality. Br. J. Ophthalmol. 2001; 85(3): 322–326.

13. Ioannidis JP. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. Cmaj. 2009; 181(8): 488–493.

14. Ioannidis J. Next-generation systematic reviews: prospective meta-analysis, individual-level data, networks and umbrella reviews. 2017.

15. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int. J. Evid. Based Healthc. 2015; 13(3): 132–140.

16. Radua J, Ramella-Cravaro V, Ioannidis JP, Reichenberg A, Phiphopthatsanee N, Amir T, et al. What causes psychosis? An umbrella review of risk and protective factors. World Psychiatry. 2018; 17(1): 49–66.

17. Raglan O, Kalliala I, Markozannes G, Cividini S, Gunter MJ, Nautiyal J, et al. Risk factors for endometrial cancer: an umbrella review of the literature. Int. J. Cancer. 2019; 145(7): 1719–1730.

18. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. Bmj. 2014; 348: g2035.

19. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. bmj. 2017; 358: j4008.

20. Veronese N, Solmi M, Caruso MG, Giannelli G, Osella AR, Evangelou E, et al. Dietary fiber and health outcomes: an umbrella review of systematic reviews and meta-analyses. Am. J. Clin. Nutr. 2018; 107(3): 436–444.

21. Veronese N, Demurtas J, Pesolillo G, Celotto S, Barnini T, Calusi G, et al. Magnesium and health outcomes: An umbrella review of systematic reviews and meta-analyses of observational and intervention studies. Eur. J. Nutr. 2020; 59(1): 263–272.

22. Machado MO, Veronese N, Sanches M, Stubbs B, Koyanagi A, Thompson T, et al. The association of depression and all-cause and cause-specific mortality: an umbrella review of systematic reviews and meta-analyses. BMC Med. 2018; 16(1): 1–13.

23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control. Clin. Trials. 1986; 7(3): 177–188.

24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003; 327(7414): 557–560.

25. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. Bmj. 2011; 342: d549.

26. Bortolato B, Köhler CA, Evangelou E, León-Caballero J, Solmi M, Stubbs B, et al. Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses. Bipolar Disord. 2017; 19(2): 84–96.

27. Dragioti E, Evangelou E, Larsson B, Gerdle B. Effectiveness of multidisciplinary programmes for clinical pain conditions: An umbrella review. J. Rehabil. Med. 2018; 50(9): 779–791.

28. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. Clin. Trials. 2007; 4(3): 245–253.

29. Ioannidis JP. Clarifications on the application and interpretation of the test for excess significance and its extensions. J. Math. Psychol. 2013; 57(5): 184–187.

30. Dragioti E, Karathanos V, Gerdle B, Evangelou E. Does psychotherapy work? An umbrella review of meta-analyses of randomized controlled trials. Acta Psychiatr. Scand. 2017; 136(3): 236–246.

31. Li X, Meng X, Timofeeva M, Tzoulaki I, Tsilidis KK, Ioannidis JP, et al. Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. Bmj. 2017; 357: j2376.

32. Akbari M, Akbari S, Pasquale LR. The association of primary open-angle glaucoma with mortality: a meta-analysis of observational studies. Arch. Ophthalmol. Chic. Ill 1960. 2009; 127(2): 204–210.

33. Marcus MW, de Vries MM, Junoy Montolio FG, Jansonius NM. Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. Ophthalmology. 2011; 118(10): 1989-1994.e2.

34. Li L, Wan X, Zhao G. Meta-analysis of the risk of cataract in type 2 diabetes. BMC Ophthalmol. 2014; 14: 94.

35. Chen X, Jhanji V, Chen C, Chen H. Serological association of Chlamydia pneumoniae infection with age-related macular degeneration: a systematic review and meta-analysis. PloS One. 2014; 9(7): e103466.

36. Zhou M, Wang W, Huang W, Zhang X. Diabetes mellitus as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. PloS One. 2014; 9(8): e102972.

37. Bae HW, Lee N, Lee HS, Hong S, Seong GJ, Kim CY. Systemic hypertension as a risk factor for open-angle glaucoma: a meta-analysis of population-based studies. PloS One. 2014; 9(9): e108226.

38. Zhao D, Cho J, Kim MH, Friedman DS, Guallar E. Diabetes, fasting glucose, and the risk of glaucoma: a meta-analysis. Ophthalmology. 2015; 122(1): 72–78.

39. Song E, Sun H, Xu Y, Ma Y, Zhu H, Pan C-W. Age-related cataract, cataract surgery and subsequent mortality: a systematic review and meta-analysis. PloS One. 2014; 9(11): e112054.

40. Au SCL, Tang S-M, Rong S-S, Chen L-J, Yam JCS. Association between hyperglycemia and retinopathy of prematurity: a systemic review and meta-analysis. Sci. Rep. 2015; 5: 9091.

41. Das R, Kerr R, Chakravarthy U, Hogg RE. Dyslipidemia and Diabetic Macular Edema: A Systematic Review and Meta-Analysis. Ophthalmology. 2015; 122(9): 1820–1827.

42. Fernandez AB, Panza GA, Cramer B, Chatterjee S, Jayaraman R, Wu W-C. Age-Related Macular Degeneration and Incident Stroke: A Systematic Review and Meta-Analysis. PloS One. 2015; 10(11): e0142968.

43. Zhou L-X, Sun C-L, Wei L-J, Gu Z-M, Lv L, Dang Y. Lower cognitive function in patients with age-related macular degeneration: a meta-analysis. Clin. Interv. Aging. 2016; 11: 215–223.

44. Chan PYL, Tang S-M, Au SCL, Rong S-S, Lau HHW, Ko STC, et al. Association of Gestational Hypertensive Disorders with Retinopathy of prematurity: A Systematic Review and Meta-analysis. Sci. Rep. 2016; 6: 30732.

45. Wang J, Xue Y, Thapa S, Wang L, Tang J, Ji K. Relation between Age-Related Macular Degeneration and Cardiovascular Events and Mortality: A Systematic Review and Meta-Analysis. BioMed Res. Int. 2016; 2016: 8212063.

46. Zhu X-R, Zhang Y-P, Bai L, Zhang X-L, Zhou J-B, Yang J-K. Prediction of risk of diabetic retinopathy for all-cause mortality, stroke and heart failure: Evidence from epidemiological observational studies. Medicine (Baltimore). 2017; 96(3): e5894.

47. McGuinness MB, Karahalios A, Finger RP, Guymer RH, Simpson JA. Age-Related Macular Degeneration and Mortality: A Systematic Review and Meta-Analysis. Ophthalmic Epidemiol. 2017; 24(3): 141–152.

48. Zhou Y, Zhang Y, Shi K, Wang C. Body mass index and risk of diabetic retinopathy: A meta-analysis and systematic review. Medicine (Baltimore). 2017; 96(22): e6754.

49. Xu C, Li J, Li Z, Mao X. Migraine as a risk factor for primary open angle glaucoma: A systematic review and meta-analysis. Medicine (Baltimore). 2018; 97(28): e11377.

50. Zhou Y, Wang C, Shi K, Yin X. Relationship between dyslipidemia and diabetic retinopathy: A systematic review and meta-analysis. Medicine (Baltimore). 2018; 97(36): e12283.

51. Zhou Y, Wang C, Shi K, Yin X. Relation of metabolic syndrome and its components with risk of diabetic retinopathy: A meta-analysis of observational studies. Medicine (Baltimore). 2018; 97(38): e12433.

52. Villamor-Martinez E, Cavallaro G, Raffaeli G, Mohammed Rahim OMM, Gulden S, Ghazi AMT, et al. Chorioamnionitis as a risk factor for retinopathy of prematurity: An updated systematic review and meta-analysis. PloS One. 2018; 13(10): e0205838.

53. Huang J, Tang Y, Zhu T, Li Y, Chun H, Qu Y, et al. Cumulative evidence for association of sepsis and retinopathy of prematurity. Medicine (Baltimore). 2019; 98(42): e17512.

54. Huon L-K, Liu SY-C, Camacho M, Guilleminault C. The association between ophthalmologic diseases and obstructive sleep apnea: a systematic review and meta-analysis. Sleep Breath. 2016; 20(4): 1145–1154.

55. Druet-Cabanac M, Boussinesq M, Dongmo L, Farnarier G, Bouteille B, Preux PM. Review of Epidemiological Studies Searching for a Relationship between Onchocerciasis and Epilepsy. Neuroepidemiology. 2004; 23(3): 144–149.

56. Wu C, You Z. Meta-analysis of the relationship between depression and diabetic retinopathy. Biomed. Res. 0970-938X. 2018; 29(9).

57. Xin X, Sun Y, Li S, Xu H, Zhang D. AGE-RELATED MACULAR DEGENERATION AND THE RISK OF ALL-CAUSE AND CARDIOVASCULAR MORTALITY: A Meta-Analysis of Cohort Studies. RETINA. 2018; 38(3). Available at: https://journals.lww.com/retinajournal/Fulltext/2018/03000/AGE_RELATED_MACULAR_DEGENERATION_AND_THE_RISK_OF.7.aspx.

58. Wang X, Tang L, Gao L, Yang Y, Cao D, Li Y. Myopia and diabetic retinopathy: a systematic review and meta-analysis. Diabetes Res. Clin. Pract. 2016; 111: 1–9.

59. Guo VY, Cao B, Wu X, Lee JJW, Zee BC. Prospective association between diabetic retinopathy and cardiovascular disease—a systematic review and meta-analysis of cohort studies. J. Stroke Cerebrovasc. Dis. 2016; 25(7): 1688–1695.

60. Chatziralli IP, Sergentanis TN. Risk Factors for Intraoperative Floppy Iris Syndrome: A Meta-Analysis. Ophthalmology. 2011; 118(4): 730–735.

61. Song D, Li C, Wang Z, Zhao Y, Shen B, Zhao W. Association of Non-alcoholic Fatty Liver Disease with Diabetic Retinopathy in Type 2 Diabetic Patients: A Meta-Analysis of Observational Studies. J. Diabetes Investig. 2020.

62. Xu X-H, Sun B, Zhong S, Wei D-D, Hong Z, Dong A-Q. Diabetic retinopathy predicts cardiovascular mortality in diabetes: a meta-analysis. BMC Cardiovasc. Disord. 2020; 20(1): 1–8.

63. Kim SJ, Port AD, Swan R, Campbell JP, Chan RVP, Chiang MF. Retinopathy of prematurity: a review of risk factors and their clinical significance. Surv. Ophthalmol. 2018; 63(5): 618–637.

64. Oh J-W, Park C-W, Moon KC, Park JS, Jun JK. The relationship among the progression of inflammation in umbilical cord, fetal inflammatory response, early-onset neonatal sepsis, and chorioamnionitis. PloS One. 2019; 14(11): e0225328–e0225328.

420 65. Bolinger MT, Antonetti DA. Moving Past Anti-VEGF: Novel Therapies for Treating Diabetic Retinopathy.
421 Int. J. Mol. Sci. 2016; 17(9).

422 66. Tsai T, Kuehn S, Tsiampalis N, Vu M-K, Kakkassery V, Stute G, et al. Anti-inflammatory cytokine and
423 angiogenic factors levels in vitreous samples of diabetic retinopathy patients. PloS One. 2018; 13(3):
424 e0194603–e0194603.

425 67. Domingueti CP, Dusse LMS, das Graças Carvalho M, de Sousa LP, Gomes KB, Fernandes AP. Diabetes
426 mellitus: the linkage between oxidative stress, inflammation, hypercoagulability and vascular
427 complications. J. Diabetes Complications. 2016; 30(4): 738–745.

428 68. Donnelly R, Emslie-Smith AM, Gardner ID, Morris AD. Vascular complications of diabetes. Bmj. 2000;
429 320(7241): 1062–1066.

430 69. Kern TS, Barber AJ. Retinal ganglion cells in diabetes. J. Physiol. 2008; 586(18): 4401–4408.

431 70. IOANNIDIS JPA. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and
432 Meta-analyses. Milbank Q. 2016; 94(3): 485–514.

433

434 Tables and Figures

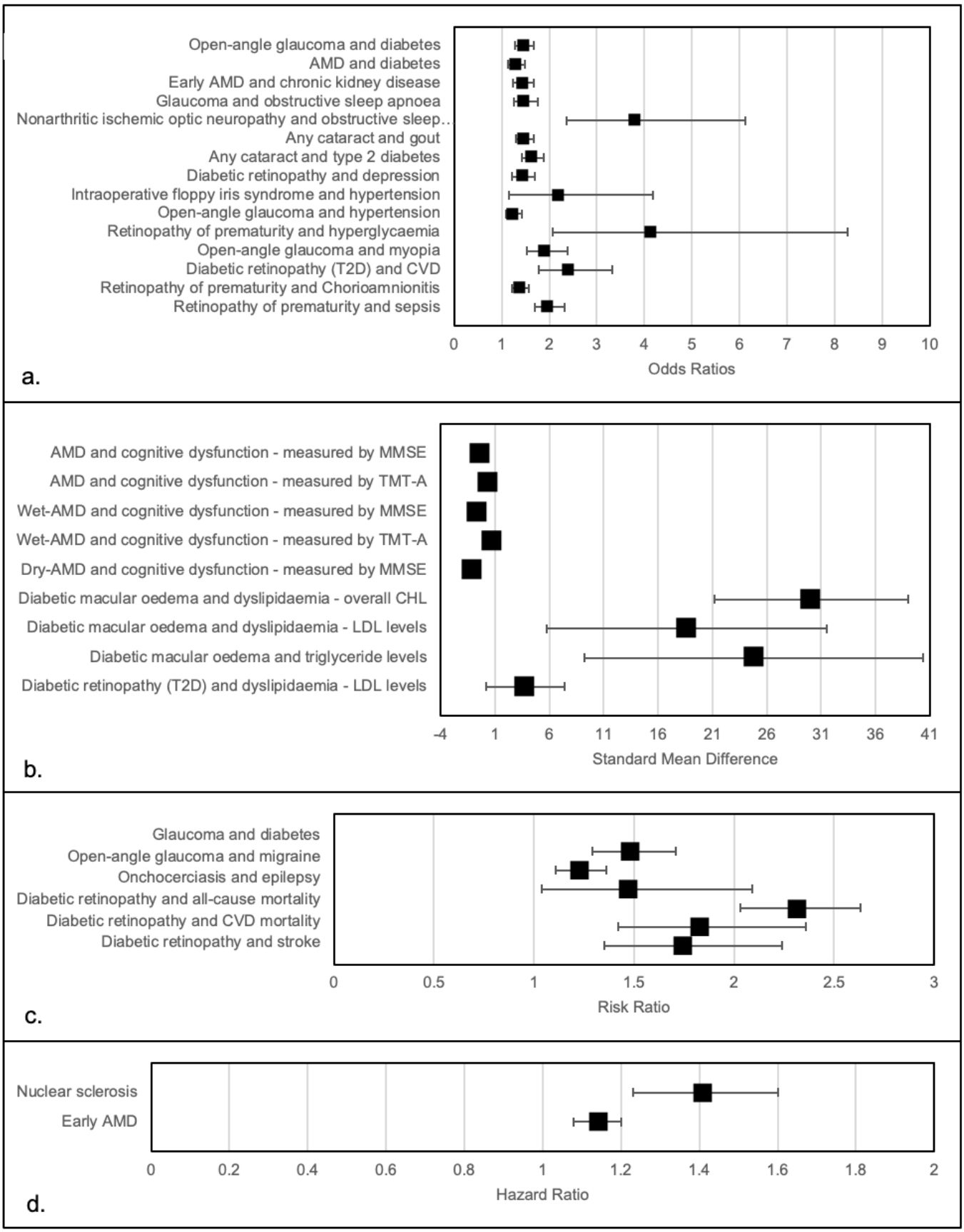

Figure 1: Significant associations between various eye diseases and health outcomes. a.= odds ratios; b.=standard mean difference; c.=risk ratio; d=hazard ratio

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	I^2	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	I^2	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?