PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of retinopathy in pre-diabetes: protocol for a systematic review and meta-analysis
AUTHORS	Kirthi, Varo; Nderitu, Paul; Alam, Uazman; Evans, Jennifer; Nevitt, Sarah; Malik, Rayaz A.; Jackson, Timothy

VERSION 1 – REVIEW

REVIEWER	John V Forrester University of Aberdeen UK
REVIEW RETURNED	14-Jun-2020

GENERAL COMMENTS	General comments The authors have designed a protocol for reviewing published data which relating to the incidence of retinopathy in prediabetic individuals. It is well recognised that patients with Type 2 diabetes may go unrecognised until they present with complications such as diabetic retinopathy and so the rationale for the study is well founded. On the other hand it is received wisdom that retinopathy does not occur until diabetes has been present for some time (often years). There is no indication of the likely yield of inclusive data. Specific comments • The diagnosis of prediabetes is based only on blood sugar level. While this is likely to capture comprehensively a large number of relevant studies, it may also include some patients who might be categorised as diabetic, while some others may be false positives. Using alternative criteria such as impaired fasting glucose and HBA1c levels may capture different subsets of patients. Have the authors considered including studies using a broader range of criteria [see Mann et al Diabetes Care (2010)] • Microvascular retinal disease occurs in other conditions associated with diabetes such as hypertension and obesity even in the presence of normoglycemia. Although data regarding these will be extracted, if retinopathy occurs in the presence of normoglycemia, how will this be considered? • two reviewers will assess selected articles. What will they assess? will there be any grading placed on the assessment?

REVIEWER	Qin Xiang Ng MOH Holdings Pte Ltd, Singapore
REVIEW RETURNED	29-Jun-2020

GENERAL COMMENTS	General comments:

	This is an interesting and much needed systematic review. I have the following minor comments for the authors to consider. Specific comments: 1. In the introduction, the authors should briefly mention the landmark UKPDS trial and that a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up (citation: N Engl J Med 2008; 359:1577-1589 doi:10.1056/NEJMoa0806470). 2. Recent studies using retinal photography to document the typical lesions of diabetic retinopathy (microaneurysms, hemorrhages, and cotton wool spots), termed isolated retinopathy signs, suggest prevalence rates in the general population of 5–10% (citation: Ophthalmology. 2003;110(4):658-666. doi:10.1016/S0161-6420(02)01931-0) and 2.6–8.6% among those without diabetes or hypertension (Diabetes Care. 2007;30(10):2708-2715. doi:10.2337/dc07-0732). Prospective study data have further shown that up to 10% of individuals aged ≥40 years without diabetes may develop these isolated retinopathy signs within 5 years (citation: Eye (Lond). 2007;21(4):465-471. doi:10.1038/sj.eye.6702771). 3. Would grey literature be searched? 4. The modified risk of bias tool should be further elaborated on. 5. As a good practice, the underlying data should be made publicly available. If this is not possible, please provide a reason why.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment 1	The authors have designed a protocol for reviewing published data which relating to the incidence of retinopathy in prediabetic individuals. It is well recognised that patients with Type 2 diabetes may go unrecognised until they present with complications such as diabetic retinopathy and so the rationale for the study is well founded. On the other hand it is received wisdom that retinopathy does not occur until diabetes has been present for some time (often years). There is no indication of the likely yield of inclusive data.
Response	We thank the reviewer for this important comment. We feel it is important to ascertain if retinopathy occurs prior to established diabetes, as a toxic environment for the development of microvascular complications is already present. We are already aware of a number of studies which meet our eligibility criteria suggestive of higher than background rates of retinopathy. We highlight a few for the perusal of the reviewer below and therefore feel it is important to determine the true prevalence of retinopathy in prediabetes (1-5). 1. Lamparter J, Raum P, Pfeiffer N, et al. Prevalence and associations of diabetic retinopathy in a large cohort of prediabetic subjects: the

	Gutenberg Health Study. *J Diabetes Complications*. 2014;28(4):482-487. doi:10.1016/j.jdiacomp.2014.02.008) 2. Diabetes Prevention Program Research Group. The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. *Diabet Med*. 2007;24(2):137-144. doi:10.1111/j.1464-5491.2007.02043.x 3. Pang C, Jia L, Jiang S, et al. Determination of diabetic retinopathy prevalence and associated risk factors in Chinese diabetic and pre-diabetic subjects: Shanghai diabetic complications study. *Diabetes Metab Res Rev*. 2012;28(3):276-283. doi:10.1002/dmrr.1307. 4. Chen X, Zhao Y, Zhou Z, et al. Prevalence and risk factors of diabetic retinopathy in Chongqing pre-diabetes patients. *Eye (Lond)*. 2012;26(6):816-820. doi:10.1038/eye.2012.50 5. Tyrberg M, Melander A, Lövestam-Adrian M, Lindblad U. Retinopathy in subjects with impaired fasting glucose: the NANSY-Eye baseline report. *Diabetes Obes Metab*. 2008;10(8):646-651. doi:10.1111/j.1463-1326.2007.00759.x

Comment 2	The diagnosis of prediabetes is based only on blood sugar level. While this is likely to capture comprehensively a large number of relevant studies, it may also include some patients who might be categorised as diabetic, while some others may be false positives. Using alternative criteria such as impaired fasting glucose and HBA1c levels may capture different subsets of patients. Have the authors considered including studies using a broader range of criteria [see Mann et al Diabetes Care (2010)].
Response	We will use internationally recognised criteria set out by the American Diabetes Association (6) and the World Health Organisation (7). Patients with pre-diabetes will be defined by the presence of IFG and/or IGT and/or A1C 5.7–6.4% (39–47 mmol/mol) as detailed by the ADA: https://care.diabetesjournals.org/content/42/Supplement_1/S13 'With regards to detection of pre-diabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1C are equally appropriate.' Where data are available, detailed sensitivity analyses will be undertaken based on diagnostic criteria (e.g. ADA vs WHO criteria) and subtype of pre-diabetes (e.g. IFG vs IGT). This is set out in lines 180-194 of the manuscript. 6. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2010 Jan;33(Suppl 1):S62–9. 7. Alberti K, Zimmet P. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med J Br Diabet Assoc. 1998 Jul;15(7):539–53.

Comment 3	Microvascular retinal disease occurs in other conditions associated with diabetes such as hypertension and obesity even in the presence of normoglycemia. Although data regarding these will be extracted, if retinopathy occurs in the presence of normoglycemia, how will this be considered?
Response	See response to comment 3 by reviewer 2 below.

Comment 4	two reviewers will assess selected articles. What will they assess? will there be any grading placed on the assessment?
Response	We apologise if this aspect of the methodology was unclear. The reviewers will assess selected articles against the eligibility criteria for inclusion into the review. We have now clarified this within the manuscript. We will not be measuring levels of agreement between the reviewers during study selection (e.g. a kappa statistic), as we feel it is important that this process is as inclusive as possible. Regarding grading, we will assess the certainty of the evidence using the GRADE approach (8,9). Specifically, we will consider prevalence studies to constitute high certainty evidence to answer this question and will downgrade for risk of bias, imprecision, inconsistency, indirectness and publication bias. Two review authors working independently will make this judgement, with arbitration by a third senior author as necessary. We have inserted this description in the methods section (lines 195-200). 8. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD 9. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ*. 2015;350:h870. Published 2015 Mar 16. doi:10.1136/bmj.h870

Reviewer 2

Comment 1	In the introduction, the authors should briefly mention the landmark UKPDS trial and that a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up (citation: N Engl J Med 2008; 359:1577-1589 doi:10.1056/NEJMoa0806470).
Response	The UKPDS trial was conducted in a cohort of individuals with recently diagnosed T2DM. It suggests that early interventions lead to long-term health benefits and questions whether interventions should be started in pre-diabetes. Our introduction focusses on pre-diabetes and we have made reference to the Da Qing study, which reported similar findings over a 30-year period in individuals with IGT. However, we anticipate expanding this topic to include diabetes in the discussion of the final output paper and will include the UKPDS study here.

Comment 2	Recent studies using retinal photography to document the typical lesions of diabetic retinopathy (microaneurysms, hemorrhages, and cotton wool spots), termed isolated retinopathy signs, suggest prevalence rates in the general population of 5–10% (citation: Ophthalmology. 2003;110(4):658-666. doi:10.1016/S0161-6420(02)01931-0) and 2.6–8.6% among those without diabetes or hypertension (Diabetes Care. 2007;30(10):2708-2715. doi:10.2337/dc07-0732). Prospective study data have further shown that up to 10% of individuals aged ≥40 years without diabetes may develop these isolated retinopathy signs within 5 years (citation: Eye (Lond). 2007;21(4):465-471. doi:10.1038/sj.eye.6702771).
Response	The prevalence of isolated retinopathy changes in normoglycaemia is an important point, but also reinforces the importance of conducting a systematic review on the prevalence in pre-diabetes. We agree that age and hypertension are potential confounding variables we have included these within the subgroup analyses to be performed (lines 158-159, 180-194).

	Thank you for the suggested citations, we have now included them in the introduction and will also use them to contextualise the findings of this review in the discussion of the final output paper. We accept that the prevalence of retinopathy may be multifactorial, but this does not detract from the clinical utility of the results in the real world, even if we cannot mechanistically determine the cause of the retinopathy e.g. via combined hypertension and dysglycaemia in people with metabolic syndrome.

Comment 3	Would grey literature be searched?
Response	We discussed this option after the reviewer's helpful suggestion. On balance, we prefer not to include a grey literature search. Whilst this may expand the body of evidence, we wish to ensure that attention is focussed on sources most likely to reveal high-quality, robust data. Hence, we will only include peer-reviewed articles from the bibliographic databases listed in lines 91-94.

Comment 4	The modified risk of bias tool should be further elaborated on.
Response	We have now included the modified risk of bias tool in full as Appendix 2. As suggested, further detail is also provided in the 'risk of bias assessment' section within the methods (lines 160-168).

Comment 5	As a good practice, the underlying data should be made publicly available. If this is not possible, please provide a reason why.
Response	We agree with the reviewer on the importance of open access data. As this review will be pooling data already in the public domain, there will be no restrictions on providing the data to those who want it. Of note, extracted data will be incorporated in a tabular format in the final output paper with appropriate referencing. Any additional data will be provided in the supplementary material.

VERSION 2 – REVIEW

REVIEWER	Qin Xiang Ng MOH Holdings Pte Ltd, Singapore
REVIEW RETURNED	10-Aug-2020

GENERAL COMMENTS	Thank you for the detailed revisions.