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Prevalence of retinopathy in pre-diabetes: protocol for a systematic review and meta-analysis

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TITLE:

Prevalence of retinopathy in pre-diabetes: protocol for a systematic review and meta-analysis

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ABSTRACT:

Introduction: There is growing evidence of a higher than expected prevalence of retinopathy in pre-diabetes. This paper presents the protocol of a systematic review and meta-analysis of

retinopathy in pre-diabetes. The aim of the review is to estimate the prevalence of retinopathy in pre-diabetes and to summarise the current data.

Methods and analysis: This protocol is developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines. A comprehensive electronic bibliographic search will be conducted in MEDLINE, EMBASE, Web of Science, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Google Scholar and the Cochrane Library. Eligible studies will report prevalence data for retinopathy on fundus photography in adults with pre-diabetes. No time restrictions will be placed on the date of publication. Screening for eligible studies and data extraction will be conducted by two reviewers independently, using defined inclusion criteria and pre-piloted data extraction forms. Disagreements between these reviewers will be resolved by a third (senior) reviewer.

The primary outcome is the prevalence of any standard features of diabetic retinopathy on fundus photography, as per International Clinical Diabetic Retinopathy Severity Scale (ICDRSS) classification. Secondary outcomes are the prevalence of: (i) any retinal microvascular abnormalities on fundus photography that are not standard features of diabetic retinopathy as per ICDRSS classification and (ii) any macular microvascular abnormalities on fundus photography, including but not limited to the presence of macular exudates, microaneurysms and haemorrhages. Risk of bias for included studies will be assessed using a validated risk of bias tool for prevalence studies. Pooled estimates for the pre-specified outcomes of interest will be calculated using random effects meta-analytic techniques. Heterogeneity will be assessed using the I^2 statistic.

Ethics and dissemination: Ethical approval is not required as this is a protocol for a systematic review and no primary data are to be collected. Findings will be disseminated through peer-reviewed publications and presentations at national and international meetings including Diabetes UK, European Association for the Study of Diabetes, American Diabetes Association and International Diabetes Federation conferences.

Registration details: This protocol has been submitted to PROSPERO for registration. Any protocol amendments will be updated on the PROSPERO database.

Abbreviations: A full list of the abbreviations used in this protocol is provided in Appendix 1.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines, provided in Appendix 2.
- This systematic review addresses an important gap in the current evidence by estimating the prevalence of retinopathy in pre-diabetes.
- There is potential for significant clinical and statistical heterogeneity in reporting of prevalence data between different populations.

BACKGROUND:

Pre-diabetes is defined by blood glucose levels above the normal range, but below the threshold for type 2 diabetes mellitus (1,2). The burden of prediabetes is enormous: it is currently estimated to affect 373 million people across the globe and this number is projected to increase to 587 million (8.3% of the global adult population) by 2045 (3).

Cohort analysis of people with pre-diabetes reveals an increased incidence of microvascular and macrovascular disease, including an elevated all-cause mortality, compared to people with normal glucose metabolism (4,5). This suggests that end-organ complications of hyperglycaemia may be occurring prior to the onset of overt diabetes (6). Furthermore, people with prediabetes and microvascular disease are more likely to develop overt diabetes (7,8). In a population-based analysis of 49,072 participants with diabetes, the presence of diabetic retinopathy (DR) was associated with an increased risk (hazard ratio 1.39, 95% confidence interval 1.09-1.76) of cardiovascular death, non-fatal myocardial infarction or stroke, after adjustment of traditional risk factors including HbA1c, lipid profile and blood pressure (9). Despite ongoing debate on how best to identify people with pre-diabetes at high risk of end-organ complications, long-term data show a reduction in both morbidity and mortality following early lifestyle interventions (10).

A systematic review of 35 population-based studies of people with diabetes reported the prevalence of DR, proliferative diabetic retinopathy (PDR), diabetic macular oedema (DMO) and vision-threatening diabetic retinopathy (VTDR) as 34.6%, 7.0%, 6.8% and 10.2%, respectively (11). The early onset of retinopathy in pre-diabetes is of particular concern as DR remains one of the principal causes of vision loss in adults of working age in developed countries, with considerable health and socioeconomic consequences (12). Given projections that up to 70% of people with pre-diabetes may eventually develop diabetes during their lifespan, early identification of retinopathy is a significant health priority (6). It is estimated that up to 95% of vision loss in diabetes is preventable or treatable, if detected early (13).

Although many studies have reported retinopathy changes in pre-diabetes, there has been no systematic review or meta-analysis of the literature to estimate an overall prevalence.

Understanding the prevalence of retinopathy may not only focus attention on early interventions but may also help refine diagnostic criteria and risk stratification for pre-diabetes. The aim of this systematic review is to estimate the prevalence of retinopathy detected on fundus photography in adults with pre-diabetes.

METHODS AND ANALYSIS:

Study design: Comprehensive literature searches of electronic bibliographic databases will be conducted in MEDLINE (access via OVID), EMBASE (access via OVID), Web of Science, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Google Scholar and the Cochrane Library. No time restrictions will be placed on the date of publication. All search strategies will be independently reviewed by an expert information specialist using the Peer Review of Electronic Search Strategies (PRESS) checklist and a draft MEDLINE search strategy is included in Appendix 3 (14). Additional articles will be identified by searching the references of included studies and other review articles identified during the course of the searches. Results from the database searches will be merged using an electronic reference manager to facilitate removal of duplicates. Trial registries such as ClinicalTrials.gov will be consulted to track studies that may not have been indexed in the databases. Relevant publications will be retrieved manually if electronic access is not available.

Participants, eligibility and setting: Inclusion criteria will be adults over 18 years of age who have pre-diabetes defined either by World Health Organisation (WHO) or American Diabetes Association (ADA) criteria (1,2). This includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) as subgroups of pre-diabetes. Population-based cohort or cross-sectional studies from any country in any setting will be considered, provided they have been

reported in English. Studies must report prevalence data for retinopathy detected on fundus photography, using any accepted method (e.g. 1-, 2-, 3- or 7-field dilated stereoscopic colour fundus photography) at least once in the study population. A lack of detail on the method used or quality of images taken will be documented but will not be considered an exclusion criterion. Studies that report other methods of imaging, such as fluorescein angiography or optical coherence tomography, will be included only if fundus photography data are also provided. A lack of reporting of the definition of diabetes and/or retinopathy will be documented but will not be considered as a reason for exclusion.

Outcomes: The primary outcome is the prevalence of any standard features of diabetic retinopathy on fundus photography, as per International Clinical Diabetic Retinopathy Severity Scale (ICDRSS) classification (15). This will be defined by the presence of any of the following features:

(i) Microaneurysms

(ii) Intraretinal haemorrhages

(iii) Hard exudates

(iv) Cotton-wool spots

(v) Venous beading

(vi) Intraretinal microvascular abnormalities (IRMAs)

(vii) New vessels at the optic disc (NVD) or elsewhere (NVE)

(viii) Vitreous or pre-retinal haemorrhage

Secondary outcomes are the prevalence of: (i) any retinal microvascular abnormalities on fundus photography that are not standard features of diabetic retinopathy as per ICDRSS

classification and (ii) any macular microvascular abnormalities on fundus photography, including but not limited to the presence of macular exudates, microaneurysms or haemorrhages.

If available, data on glycaemic parameters such as fasting glucose, two-hour oral glucose tolerance test (OGTT) and HbA1c will be extracted. Similarly, if reported, prevalence data on cardiovascular parameters such as systolic and diastolic blood pressure, lipid profile and metabolic syndrome will also be extracted. Metabolic syndrome will be defined as per consensus criteria based on WHO, National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and ADA classifications (2,16–19).

Study selection: Two reviewers will independently screen titles and abstracts from the searches. Any disagreements will be resolved by discussion with a third (senior) reviewer. Articles of interest will be selected for a full-text assessment. If there is any doubt regarding the eligibility of a study, the article will be selected for full-text assessment.

Two reviewers will independently assess the full text articles. Disagreements between these reviewers will be resolved by discussion and where necessary, with a third (senior) reviewer, to decide if the article is eligible for inclusion.

A PRISMA flowchart of the selection process will be included in the systematic review (20).

Data collection process: Two reviewers will independently extract data in duplicate using pre-piloted forms. Data recorded will include: (i) date and country of study; (ii) study design; (iii) age, gender and ethnicity of participants; (iv) definition of retinopathy and method(s) used to obtain images; (v) definition of pre-diabetes and method(s) used to make diagnosis; (vi) study

groups and sizes; (vii) overall sample size and (viii) prevalence number and estimate. If present, secondary outcome data will also be recorded, including (i) definition and prevalence of non-standard retinopathy features and (ii) definition and prevalence of maculopathy features. Where reported, prevalence estimates for co-morbid ocular pathology (e.g. cataract) and cardiovascular risk factors (e.g. hypertension, metabolic syndrome) will also be recorded.

Risk of bias assessment: A modified critical appraisal tool for specifically assessing risk of bias in prevalence studies will be used on selected articles (21). Quality assessment will be undertaken by two reviewers independently. Disagreements will be resolved by discussion or referral to a third (senior) reviewer. Judgements on the overall risk of bias will be categorised as either low, moderate or high risk, based on the risk of bias of the 10 individual items listed within the tool.

Data analysis: Data will be analysed using purpose-built software for systematic reviews and meta-analyses (Review Manager 5). Heterogeneity between included studies will be assessed based on study design, populations and methods used to measure outcomes. Statistical heterogeneity will be assessed using the I^2 statistic and by visual inspection of forest plots.

Characteristics of included studies will be presented in summary tables and narrative text. In expectation of prevalence varying between studies and populations, pooled prevalence estimates for the pre-specified outcomes of interest will be calculated applying random effects meta-analytic methods and reported in forest plots.

Where clinical and/or statistical heterogeneity is deemed too large by the reviewers (e.g. $I^2 \geq$ 90%), a systematic review without meta-analysis will be reported. Narrative synthesis will be conducted where quantitative data required for meta-analysis is lacking or absent.

Depending on availability of data, subgroup analyses using the following covariates will also be considered:

- WHO region or country
- Study period
- Age group (e.g. 18-30, 31-50, >50 years)
- Ethnicity (especially at-risk groups e.g. South Asian, African, Afro-Caribbean, Hispanic)
- Time since diagnosis of pre-diabetes (e.g. <1 year, 1-5 years, 6-10 years, >10 years)
- Grade of retinopathy as per ICDRSS classification
- Co-morbid ocular pathology (e.g. cataract)
- Co-morbid cardiovascular risk factors (e.g. hypertension, metabolic syndrome)
- Method used to diagnose pre-diabetes (e.g. OGTT)
- Method used to diagnose retinopathy (e.g. 7-field stereoscopic imaging)

If sufficient data are available, a sensitivity analysis will be performed excluding studies judged to be at high risk of bias.

PATIENT AND PUBLIC INVOLVEMENT:

There were no time or funds allocated to patient and public involvement, particularly in the context of the current coronavirus pandemic, so the reviewers were unable to involve patients. However, this systematic review asks an important clinical question and the protocol

described follows a standardised approach as per PRISMA-P guidelines. People with pre-diabetes will be invited to help the reviewers develop a strategy to disseminate the results.

ETHICS AND DISSEMINATION:

This study is a systematic review using aggregated published data, without accessing any personal identifiable information, hence there are no significant ethical or safety concerns. The results of this study will be presented at international conferences and submitted for publication in a peer-reviewed open-access journal. Authors will use their networks to encourage broad dissemination of the results.

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AUTHORS' CONTRIBUTIONS:

VK, UA and TLJ conceived the review topic. VK performed background exploratory searches and drafted the initial search strategy. VK, JE and PN co-wrote the initial protocol. UA, SN, RAM and TLJ provided critical appraisal and senior oversight of the protocol.

For the systematic review, VK and PN will perform the searches, data extraction and analysis. JE will provide oversight of the searches, data analysis and extraction. SN will provide statistical input for data analysis. UA, RAM and TLJ will provide critical appraisal and senior oversight of the final manuscript.

FUNDING STATEMENT:

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COMPETING INTERESTS STATEMENT:

The authors have no competing interests to declare.

KEY WORDS:

Pre-diabetes, retinopathy, systematic review, humans.

WORD COUNT:

2,288 (excluding references and appendices)

APPENDIX 1 – LIST OF ABBREVIATIONS:

ADA	American Diabetes Association
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DR	Diabetic Retinopathy
DMO	Diabetic Macular Oedema
ICDRSS	International Clinical Diabetic Retinopathy Severity Scale
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IRMA	Intra-Retinal Microvascular Abnormalities
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NSC	National Screening Committee (United Kingdom)
NVD	New Vessels at the Disc
NVE	New Vessels Elsewhere
OGTT	Oral Glucose Tolerance Test
PRESS	Peer Review of Electronic Search Strategies
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PDR	Proliferative Diabetic Retinopathy
VTDR	Vision-Threatening Diabetic Retinopathy
WHO	World Health Organisation

APPENDIX 3 – DRAFT MEDLINE SEARCH STRATEGY:

1. exp Prevalence/
2. exp Incidence/
3. exp Epidemiology/
4. exp Epidemiologic Methods/
5. exp Population Characteristics/
6. (prevalen* or occur* or inciden* or burden or epidemiolog* or frequenc* or rate).tw
7. Or/1-6
8. exp Glucose Intolerance/
9. exp Prediabetic State/
10. exp Hyperglycemia/
11. exp Glycated Hemoglobin A/
12. glucose intolerance.tw
13. (prediabet* or pre-diabet* or pre diabet* or borderline diabet*).tw
14. hyperglyc?emi*.tw
15. ((impaired fasting adj2 glucose) or IFG or impaired FPG).tw
16. ((impaired glucose adj (tolerance or metabolism)) or IGT).tw
17. Or/8-16
18. exp Diabetic Retinopathy/
19. exp Retina/
20. microvasc* adj2 (change* or disease* or dysfuncti* or complicat*).tw
21. (retinopathy or retinal).tw
22. Or/18-21
23. 7 and 17 and 22

24. exp animals/ not humans.sh

25. 23 not 24

26. ..dedup 25

APPENDIX 2 – PRISMA-P 2015 CHECKLIST

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	☐	N/A
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-16
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	264-271
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	46-47
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	N/A
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	56-87

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	86-87
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	101-113
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	88-100
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	92-95
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	161-164
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	137-144
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	145-146
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	146-154
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	114-136
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	155-160
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	161-168
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	169-171

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	172-185
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	169-171
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	184-185
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☐	N/A

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Secondary Subject Heading:	Ophthalmology, Epidemiology
Keywords:	Diabetic retinopathy < DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, Medical retina < OPHTHALMOLOGY, EPIDEMIOLOGY

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TITLE:

Prevalence of retinopathy in pre-diabetes: protocol for a systematic review and meta-analysis

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ABSTRACT:

Introduction: There is growing evidence of a higher than expected prevalence of retinopathy in pre-diabetes. This paper presents the protocol of a systematic review and meta-analysis of

retinopathy in pre-diabetes. The aim of the review is to estimate the prevalence of retinopathy in pre-diabetes and to summarise the current data.

Methods and analysis: This protocol is developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines. A comprehensive electronic bibliographic search will be conducted in MEDLINE, EMBASE, Web of Science, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Google Scholar and the Cochrane Library. Eligible studies will report prevalence data for retinopathy on fundus photography in adults with pre-diabetes. No time restrictions will be placed on the date of publication. Screening for eligible studies and data extraction will be conducted by two reviewers independently, using defined inclusion criteria and pre-piloted data extraction forms. Disagreements between the reviewers will be resolved by discussion, and if required, a third (senior) reviewer will arbitrate.

The primary outcome is the prevalence of any standard features of diabetic retinopathy on fundus photography, as per International Clinical Diabetic Retinopathy Severity Scale (ICDRSS) classification. Secondary outcomes are the prevalence of: (i) any retinal microvascular abnormalities on fundus photography that are not standard features of diabetic retinopathy as per ICDRSS classification and (ii) any macular microvascular abnormalities on fundus photography, including but not limited to the presence of macular exudates, microaneurysms and haemorrhages. Risk of bias for included studies will be assessed using a validated risk of bias tool for prevalence studies. Pooled estimates for the pre-specified outcomes of interest will be calculated using random effects meta-analytic techniques. Heterogeneity will be assessed using the I^2 statistic.

Ethics and dissemination: Ethical approval is not required as this is a protocol for a systematic review and no primary data are to be collected. Findings will be disseminated through peer-reviewed publications and presentations at national and international meetings including Diabetes UK, European Association for the Study of Diabetes, American Diabetes Association and International Diabetes Federation conferences.

Registration details: This review has been registered on PROSPERO (ID: CRD42020184820). Any protocol amendments will be updated on the PROSPERO database.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.
- This systematic review addresses an important gap in the current evidence by estimating the prevalence of retinopathy in pre-diabetes.
- There is potential for significant clinical and statistical heterogeneity in reporting of prevalence data between different populations.

BACKGROUND:

Pre-diabetes is defined by blood glucose levels above the normal range, but below the threshold for type 2 diabetes mellitus (1,2). The burden of prediabetes is enormous: it is currently estimated to affect 373 million people across the globe and this number is projected to increase to 587 million (8.3% of the global adult population) by 2045 (3).

Cohort analysis of people with pre-diabetes reveals an increased incidence of microvascular and macrovascular disease, including an elevated all-cause mortality, compared to people with normal glucose metabolism (4,5). This suggests that end-organ complications of hyperglycaemia may be occurring prior to the onset of overt diabetes (6). Furthermore, people with prediabetes and microvascular disease are more likely to develop overt diabetes (7,8). In a population-based analysis of 49,072 participants with diabetes, the presence of diabetic retinopathy (DR) was associated with an increased risk (hazard ratio 1.39, 95% confidence interval 1.09-1.76) of cardiovascular death, non-fatal myocardial infarction or stroke, after adjustment of traditional risk factors including HbA1c, lipid profile and blood pressure (9). Despite ongoing debate on how best to identify people with pre-diabetes at high risk of end-organ complications, long-term data show a reduction in both morbidity and mortality following early lifestyle interventions (10).

A systematic review of 35 population-based studies of people with diabetes reported the prevalence of DR, proliferative diabetic retinopathy (PDR), diabetic macular oedema (DMO) and vision-threatening diabetic retinopathy (VTDR) as 34.6%, 7.0%, 6.8% and 10.2%, respectively (11). The early onset of retinopathy in pre-diabetes is of particular concern as DR remains one of the principal causes of vision loss in adults of working age in developed countries, with considerable health and socioeconomic consequences (12). Given projections that up to 70% of people with pre-diabetes may eventually develop diabetes during their lifespan, early identification of retinopathy is a significant health priority (6). It is estimated that up to 95% of vision loss in diabetes is preventable or treatable, if detected early (13).

Previous studies have suggested that isolated retinopathy changes occur in 5-10% of the general population and in 2.6-8.6% in those without diabetes or hypertension (14,15).

Although several studies have reported retinopathy changes in pre-diabetes, there has been no systematic review or meta-analysis of the literature to estimate an overall prevalence. Understanding the prevalence of retinopathy may not only focus attention on early interventions but may also help refine diagnostic criteria and risk stratification for pre-diabetes. The aim of this systematic review is to estimate the prevalence of retinopathy detected on fundus photography in adults with pre-diabetes.

METHODS AND ANALYSIS:

Study design: Comprehensive literature searches of electronic bibliographic databases will be conducted in MEDLINE (access via OVID), EMBASE (access via OVID), Web of Science, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Google Scholar and the Cochrane Library. No time restrictions will be placed on the date of publication. All search strategies will be independently reviewed by an expert information specialist using the Peer Review of Electronic Search Strategies (PRESS) checklist and a draft MEDLINE search strategy is included in Appendix 1 (16). Additional articles will be identified by searching the references of included studies and other review articles identified during the course of the searches. Results from the database searches will be merged using an electronic reference manager to facilitate removal of duplicates. Trial registries such as ClinicalTrials.gov will be consulted to track studies that may not have been indexed in the databases. Relevant publications will be retrieved manually if electronic access is not available.

Participants, eligibility and setting: Inclusion criteria will be adults over 18 years of age who have pre-diabetes defined by American Diabetes Association (ADA) criteria (1). This includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) as subgroups of pre-

diabetes. Population-based cohort or cross-sectional studies from any country in any setting will be considered, provided they have been reported in English. Studies must report prevalence data for retinopathy detected on fundus photography, using any accepted method (e.g. 1-, 2-, 3- or 7-field dilated stereoscopic colour fundus photography) at least once in the study population. A lack of detail on the method used or quality of images taken will be documented but will not be considered an exclusion criterion. Studies that report other methods of imaging, such as fluorescein angiography or optical coherence tomography, will be included only if fundus photography data are also provided. Use of alternative diagnostic criteria for pre-diabetes, such as World Health Organization (WHO) criteria, will be recorded and prevalence figures reported separately, but will not be considered a reason for exclusion (2). A lack of reporting of the definition of pre-diabetes and/or retinopathy will be documented but will not be considered a reason for exclusion.

Outcomes: The primary outcome is the prevalence of any standard features of diabetic retinopathy on fundus photography, as per International Clinical Diabetic Retinopathy Severity Scale (ICDRSS) classification (17). This will be defined by the presence of any of the following features:

(i) Microaneurysms

(ii) Intraretinal haemorrhages

(iii) Hard exudates

(iv) Cotton-wool spots

(v) Venous beading

(vi) Intraretinal microvascular abnormalities (IRMAs)

(vii) New vessels at the optic disc (NVD) or elsewhere (NVE)

(viii) Vitreous or pre-retinal haemorrhage

Secondary outcomes are the prevalence of: (i) any retinal microvascular abnormalities on fundus photography that are not standard features of diabetic retinopathy as per ICDRSS classification and (ii) any macular microvascular abnormalities on fundus photography, including but not limited to the presence of macular exudates, microaneurysms or haemorrhages.

If available, data on glycaemic parameters such as fasting glucose, two-hour oral glucose tolerance test (OGTT) and HbA1c will be extracted. Similarly, if reported, prevalence data on cardiovascular parameters such as systolic and diastolic blood pressure, lipid profile and metabolic syndrome will also be extracted. Metabolic syndrome will be defined as per consensus criteria based on WHO, National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and ADA classifications (2,18–21).

Study selection: Two reviewers will independently screen titles and abstracts from the searches and exclude any that clearly do not satisfy the inclusion criteria. Any disagreements will be resolved by discussion, and if required, a third (senior) reviewer will arbitrate. Articles of interest will be selected for a full-text assessment. If there is any doubt regarding the eligibility of a study, the article will be selected for full-text assessment.

Two reviewers will independently assess the full text articles against the eligibility criteria. Disagreements between these reviewers will be resolved by discussion, and if required, a third (senior) reviewer will arbitrate.

A PRISMA flowchart of the selection process will be included in the systematic review (22).

Data collection process: Two reviewers will independently extract data in duplicate using pre-piloted forms. Data recorded will include: (i) date and country of study; (ii) study design; (iii) age, gender and ethnicity of participants; (iv) definition of retinopathy and method(s) used to obtain images; (v) definition of pre-diabetes and method(s) used to make diagnosis; (vi) study groups and sizes; (vii) overall sample size and (viii) prevalence number and estimate. If present, secondary outcome data will also be recorded, including (i) definition and prevalence of non-standard retinopathy features and (ii) definition and prevalence of maculopathy features. Where reported, prevalence estimates for co-morbid ocular pathology (e.g. cataract) and cardiovascular risk factors (e.g. hypertension, metabolic syndrome) will also be recorded.

Risk of bias assessment: A modified critical appraisal tool for specifically assessing risk of bias in prevalence studies will be used on selected articles and is included in Appendix 2 (23). The tool includes 9 questions, each scoring 0 or 1, to determine confounding, selection bias, and bias related to measurement and data analysis. Overall risk of bias will be determined by the total score for each article: 0-3 considered low risk, 4-6 considered moderate risk and ≥7 considered high risk. Quality assessment will be undertaken by two reviewers independently. Disagreements will be resolved by discussion, and if required, a third (senior) reviewer will arbitrate. Judgements on the overall risk of bias will be categorised as either low, moderate or high risk, based on the risk of bias of the 10 individual items listed within the tool.

Data analysis: Data will be analysed using purpose-built software for systematic reviews and meta-analyses (Review Manager 5). Heterogeneity between included studies will be assessed based on study design, populations and methods used to measure outcomes. Statistical heterogeneity will be assessed using the I^2 statistic and by visual inspection of forest plots.

Characteristics of included studies will be presented in summary tables and narrative text. In expectation of prevalence varying between studies and populations, pooled prevalence estimates for the pre-specified outcomes of interest will be calculated applying random effects meta-analytic methods and reported in forest plots.

Where clinical and/or statistical heterogeneity is deemed too large by the reviewers (e.g. $I^2 \geq 90\%$), a systematic review without meta-analysis will be reported. Narrative synthesis will be conducted where quantitative data required for meta-analysis is lacking or absent.

Depending on availability of data, subgroup analyses using the following covariates will also be considered:

- WHO region or country
- Study period
- Age group (e.g. 18-30, 31-50, >50 years)
- Ethnicity (especially at-risk groups e.g. South Asian, African, Afro-Caribbean, Hispanic)
- Time since diagnosis of pre-diabetes (e.g. <1 year, 1-5 years, 6-10 years, >10 years)
- Subtype of pre-diabetes (e.g. IFG compared to IGT)
- Grade of retinopathy as per ICDRSS classification
- Co-morbid ocular pathology (e.g. cataract)
- Co-morbid cardiovascular risk factors (e.g. hypertension, metabolic syndrome)
- Method or criteria used to diagnose pre-diabetes (e.g. WHO)
- Method used to diagnose retinopathy (e.g. 7-field stereoscopic imaging)

If sufficient data are available, a sensitivity analysis will be performed excluding studies judged to be at high risk of bias.

Grading of evidence: Certainty of the evidence will be assessed using the GRADE approach (24,25). Specifically, prevalence studies will be considered to constitute high certainty evidence to answer this review question, and downgraded for risk of bias, imprecision, inconsistency, indirectness and publication bias. Two reviewers will independently make this judgement. Disagreements will be resolved by discussion, and if required, a third (senior) reviewer will arbitrate.

PATIENT AND PUBLIC INVOLVEMENT:

There were no time or funds allocated to patient and public involvement, particularly in the context of the current coronavirus pandemic, so the reviewers were unable to involve patients. However, this systematic review asks an important clinical question and the protocol described follows a standardised approach as per PRISMA-P guidelines. People with pre-diabetes will be invited to help the reviewers develop a strategy to disseminate the results.

ETHICS AND DISSEMINATION:

This study is a systematic review using aggregated published data, without accessing any personal identifiable information, hence there are no significant ethical or safety concerns. The results of this study will be presented at international conferences and submitted for publication in a peer-reviewed open-access journal. Authors will use their networks to encourage broad dissemination of the results.

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AUTHORS' CONTRIBUTIONS:

VK, UA and TLJ conceived the review topic. VK performed background exploratory searches and drafted the initial search strategy. VK, JE and PN co-wrote the initial protocol. UA, SN, RAM and TLJ provided critical appraisal and senior oversight of the protocol.

For the systematic review, VK and PN will perform the searches, data extraction and analysis. JE will provide oversight of the searches, data analysis and extraction. SN will provide statistical input for data analysis. UA, RAM and TLJ will provide critical appraisal and senior oversight of the final manuscript.

FUNDING STATEMENT:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT:

The authors have no competing interests to declare.

KEY WORDS:

Pre-diabetes, retinopathy, systematic review, humans.

PLANNED START DATE:

1 August 2020

PLANNED END DATE:

31 January 2021

WORD COUNT:

2,474 (excluding references and appendices)

APPENDIX 1 – DRAFT MEDLINE SEARCH STRATEGY:

1. exp Prevalence/
2. exp Incidence/
3. exp Epidemiology/
4. exp Epidemiologic Methods/
5. exp Population Characteristics/
6. (prevalen* or occur* or inciden* or burden or epidemiolog* or frequenc* or rate).tw
7. Or/1-6
8. exp Glucose Intolerance/
9. exp Prediabetic State/
10. exp Hyperglycemia/
11. exp Glycated Hemoglobin A/
12. glucose intolerance.tw
13. (prediabet* or pre-diabet* or pre diabet* or borderline diabet*).tw
14. hyperglyc?emi*.tw
15. ((impaired fasting adj2 glucose) or IFG or impaired FPG).tw
16. ((impaired glucose adj (tolerance or metabolism)) or IGT).tw
17. Or/8-16
18. exp Diabetic Retinopathy/
19. exp Retina/
20. microvasc* adj2 (change* or disease* or dysfuncti* or complicat*).tw
21. (retinopathy or retinal).tw
22. Or/18-21
23. 7 and 17 and 22

24. exp animals/ not humans.sh

25. 23 not 24

26. ..dedup 25

APPENDIX 2 – CRITICAL APPRAISAL TOOL FOR PREVALENCE STUDIES USED BY HOY ET AL. (2012):

Name of author(s): **Year of publication:** **Study title:**			
Risk of bias items		**Risk of bias levels**	**Points scored**
1	Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	**Yes (LOW RISK):** The study's target population was a close representation of the national population.	**0**
		No (HIGH RISK): The study's target population was clearly NOT representative of the national population.	**1**
2	Was the sampling frame a true or close representation of the target population?	**Yes (LOW RISK):** The sampling frame was a true or close representation of the target population.	**0**
		No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	**1**
3	Was some form of random selection used to select the sample, OR, was a census undertaken?	**Yes (LOW RISK):** A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	**0**
		No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	**1**
4	Was the likelihood of non-response bias minimal?	**Yes (LOW RISK):** The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non- responders	**0**
		No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders.	**1**
5	Were data collected directly from the subjects (as opposed to a proxy)?	**Yes (LOW RISK):** All data were collected directly from the subjects.	**0**
		No (HIGH RISK): In some instances, data were collected from a proxy.	**1**
6	Was an acceptable case definition used in the study?	**Yes (LOW RISK):** An acceptable case definition was used.	**0**
		No (HIGH RISK): An acceptable case definition was NOT used.	**1**
7	Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	**Yes (LOW RISK):** The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.	**0**
		No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	**1**
8	Was the same mode of data collection Yes (LOW RISK): The same mode of data collection was used for all 0 used for all subjects?	**Yes (LOW RISK):** The same mode of data collection was used for all subjects.	**0**
		No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	**1**
9	Were the numerator(s) and denominator(s) for the	**Yes (LOW RISK):** The paper presented appropriate numerator(s) AND denominator(s) for the parameter of	**0**

	appropriate	interest (e.g. the prevalence of low back pain).	
		No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	**1**
10	Summary on the overall risk of study bias	**LOW RISK**	**0-3**
		MODERATE RISK	**4-6**
		HIGH RISK	**7-9**

SUPPLEMENTAL FILE – PRISMA-P 2015 CHECKLIST

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted – **Moher D, Stewart L & Shekelle P:** Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	47-48
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-16
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	291-298
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	47-48
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	N/A
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	56-89

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	88-89
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	103-117
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	91-102
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	94-97
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	169-170
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	141-149
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	150-151
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	151-159
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	118-140
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	160-168
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	169-172
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	173-176
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	180-192
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	177-179

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	193-194
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	195-200