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The prevalence of retinopathy in prediabetes: a systematic review

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Abstract:	Diabetic retinopathy is a leading cause of vision loss globally. The current diagnostic thresholds for diabetes are still based on historic data correlating glycaemic parameters with retinopathy. However, an excess prevalence of retinopathy has also been reported in prediabetes. This systematic review aimed to determine the reported prevalence of retinopathy in adults with prediabetes. We performed searches using MEDLINE, EMBASE, PubMed, Web of Science, CINAHL, Google Scholar and the Cochrane databases from inception to 1 August 2020. We evaluated methodological quality and certainty of the evidence using a validated risk of bias tool and GRADE, respectively. Twenty-four studies (8759 participants with prediabetes) were included after screening 5994 abstracts and reviewing 98 full-text records. Nineteen studies (79%) reported population-based data. Retinopathy prevalence estimates ranged between 0.3-14.1% (median 7.1%, interquartile range 2.4-10.0%), with high variance in estimates due to differing screening methods, retinopathy grading protocols and study populations. We judged this as low-certainty evidence using GRADE, downgrading for risk of bias and inconsistency. From studies that compared both populations, post hoc analysis revealed a lower median retinopathy prevalence in normal glucose tolerance (3.2%, interquartile range 0.3-7.3%) than prediabetes (6.6%, interquartile range 1.9-9.8%). These data suggest an excess prevalence of retinopathy in prediabetes.
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TITLE

The prevalence of retinopathy in prediabetes: Aa systematic review

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KEY WORDS

Prediabetes, impaired fasting glucose, impaired glucose tolerance, retinopathy, prevalence, epidemiology

ABSTRACT

Diabetic retinopathy is a leading cause of vision loss globally. The current diagnostic thresholds for diabetes are still based on historic data correlating glycaemic parameters with retinopathy; h~~. H~~owever, an excess prevalence of retinopathy has also been reported in prediabetes. ~~This systematic review~~We aimed to determine the reported prevalence of retinopathy in adults with prediabetes. We performed searches using MEDLINE, EMBASE, PubMed, Web of Science, CINAHL, Google Scholar and the Cochrane databases from inception to 1 August 2020. We evaluated methodological quality and certainty of the evidence using a validated risk of bias tool and GRADE, respectively. Twenty-four studies (8759 participants with prediabetes) were included after screening 5994 abstracts and reviewing 98 full-text records. Nineteen studies (79%) reported population-based data. Retinopathy prevalence estimates ranged between 0.3-14.1% (median 7.1%, interquartile range 2.4-10.0%), with high variance in estimates due to differing screening methods, retinopathy grading protocols and study populations. We judged this as low-certainty evidence using GRADE, downgrading for risk of bias and inconsistency. From studies that compared both populations, *post hoc* analysis revealed a lower median retinopathy prevalence in normal glucose tolerance (3.2%, interquartile range 0.3-7.3%) than prediabetes (6.6%, interquartile range 1.9-9.8%). These data suggest an excess prevalence of retinopathy in prediabetes.

1. INTRODUCTION

Prediabetes is defined as suboptimal glyc~~a~~emia ~~which~~ that does not reach the threshold for type 2 diabetes [1,4]. Worldwide, approximately one in 13 adults (374 million) aged 20-79 years have prediabetes, and the vast majority are unaware of the diagnosis [23]. There is a significant predicted burden, with the International Diabetes Federation projecting 587 million people (8.3% of adults) to have prediabetes by 2045 [23].

The World Health Organization (WHO) uses two specific parameters to define prediabetes: (i) impaired fasting glucose (IFG), defined as a fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110-125 mg/dL) and (ii) impaired glucose tolerance (IGT), defined as a two-hour plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dL) after ingestion of 75g oral glucose, or a combination of the two based on a two-hour oral glucose tolerance test (OGTT) [1]. The American Diabetes Association (ADA) uses the same cut-off value for IGT (140-200 mg/dL), but has a lower cut-off value for IFG (100-125 mg/dL) [4]. In addition, the ADA includes a haemoglobin A1c (HbA1c) level of 5.7-6.4% to define prediabetes [4].

Current diagnostic thresholds for fasting and two-hour post-load plasma glucose levels are based on the presence of retinopathy reported in population-based studies in Pima Indians, Egypt, and the United States; [53] h~~. H~~owever, subsequent studies have failed to confirm these thresholds, attributed to broad definitions of retinopathy and limited statistical power [52,61]. The DETECT-2 study showed that diabetic retinopathy (DR) was associated with a fasting plasma glucose of 6.5 mmol/l [10]. Data also suggest that end-organ complications occur prior to the onset of type 2 diabetes [50]. Compared to individuals with normal glucose tolerance (NGT), those with prediabetes have an increased prevalence of microvascular disease, elevated all-cause mortality, and a doubling of coronary heart disease mortality [51,57]. People with

prediabetes and concomitant microvascular disease are also more likely to develop type 2 diabetes [5,30,58].

In people with diabetes, the worldwide prevalence of any DR, proliferative DR, diabetic macular ~~o~~edema and vision-threatening DR is 34.6%, 7.0%, 6.8% and 10.2%, respectively [63]. Hence the early diagnosis of sight-threatening disease is key [38,50]. Although approaches to population-based screening vary by country, digital retinal photography is considered the most effective screening method for DR [62]. Although isolated retinopathy occurs with increasing age and hypertension, the prevalence varies between 2.6-8.6% even in individuals without diabetes or hypertension, which may be attributed to prediabetes [39,60]. We aimed to determine and discuss the prevalence of retinopathy in prediabetes by undertaking a systematic review of published data, using evidence-based Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2. RESULTS

2.1 Study characteristics: After removal of duplicate entries, we identified 5155 records from the electronic database searches and selected 98 records for full-text review. Of these, 24 studies (8759 participants with prediabetes) were included in the final review. Reasons for exclusion after full-text review are shown in Figure 1.

Characteristics of the included studies are presented in Table 1. Of the 15 studies that reported age data, 11 reported a mean or median age of participants. Among the 21 studies that reported gender data, gender ratios varied widely from 17.9% to 67.8% male.

Studies were conducted in 22 different countries and 6 ~~six~~ WHO regions. Eight studies were conducted in Europe, 6 ~~six~~ in the Americas (USA), six in the Western Pacific (China, Japan, Singapore, Australia and Samoa), and 1 each ~~one~~ in South-East Asia (Bangladesh), ~~one in~~ Africa (Mauritius) and ~~one in~~ the Eastern Mediterranean (Egypt). One publication was a multinational study conducted across 9 ~~nine~~ countries [16]. Thirteen studies reported race or ethnicity data, from a wide variety of backgrounds; 2~~two~~ studies exclusively examined African Americans and Pima Indians, both from the USA [35,43]. The majority of studies were cross-sectional and population-based (19/24, 79%); three were cross-sectional, hospital-based studies and two were double-blind, randomised-controlled trials reporting baseline prevalence data. Sample sizes for the included studies varied between 34 and 960. Fifteen studies used WHO criteria to define prediabetes~~;~~, five used ADA criteria, two used non-standard or superseded WHO criteria, 1~~one~~ failed to report how prediabetes was defined, and 1~~one~~ study used stricter non-standard IFG criteria [54].

2.2 Risk of bias assessment: Points scored on individual risk of bias items and the overall scores of the included studies are provided in Table S1. We deemed the majority of studies

(19/24, 79%) 'low' risk whilst the remaining five were deemed 'moderate' risk. The most common issues were: (i) the likelihood of non-response bias due to a response rate <75% (17 studies); (ii) the study instrument not shown to have reliability or validity, scored for any study that failed to perform pharmacological mydriasis (14 studies) and (iii) a lack of census or some form of random selection performed to select the sample (9 studies).

~~Due~~ Owing to variations in study populations, fields captured on retinal photography, retinopathy classifications, use of pharmacological dilation and diagnostic methods for prediabetes, we considered clinical and statistical (I^2: 93%) heterogeneity too high to perform a meta-analysis [20]. Where quantitative data were available, we recorded median estimates and ranges. Where such data were lacking, we conducted a narrative analysis of the data.

2.3 Primary outcome: A summary of the prevalence data is shown in Figure 2 and Table 2. The median estimated prevalence of retinopathy in prediabetes was 7.1% (interquartile range (IQR): 2.4-9.7%); h~~. H~~owever, prevalence estimates varied widely, from 0.3% in a study from the Netherlands (n=478)~~,~~ to 14.1% in a study from Japan (n=303) [19,26]. The median sample size for the at-risk population with prediabetes was 235 (range 34-960).

2.4 GRADE assessment of primary outcome: Confidence in the body of evidence for the primary outcome was assessed using the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) domains: (i) risk of bias, (ii) inconsistency, (iii) imprecision, (iv) indirectness and (v) publication bias, summarised in Table S2. Although the overall risk of bias in most studies was low, the majority of studies were at risk of non-response bias and a significant proportion reported non-random sampling methods. There was also evidence of inconsistency due to a wide variation in prevalence estimates, which did not correlate with study settings. Although 95% confidence intervals for most prevalence estimates

were wide, given the total number of participants, if data were pooled the overall estimate of prevalence may be reasonably precise. As the majority of studies were population-based and all studies measured the outcome of interest, we found no evidence of indirectness. Although studies of varying sample sizes reported high and low prevalence estimates, we found no evidence of publication bias. We deemed the overall GRADE assessment of the prevalence of retinopathy in prediabetes low certainty, downgrading one level for risk of bias and one level for inconsistency.

2.5 Subgroup analyses of primary outcome: Where quantitative subgroup data were lacking, we conducted a narrative analysis. As insufficient data were reported, we did not perform an analysis of the time since diagnosis of prediabetes on the prevalence of retinopathy.

2.5.1 WHO region: Median retinopathy estimates by WHO region were 7.6% (range: 1.4-12.0%) for the Americas, 8.9% (range: 0.3-11.0%) for Europe and 6.8% (range: 1.4-14.1%) for the Western Pacific. Only ~~one~~ 1 study contributed to the retinopathy estimates for Africa (9.1%), South-East Asia (13.0%), and the Eastern Mediterranean (1.9%).

2.5.2 Age, gender and ethnicity: Two studies reported age-specific prevalence estimates in prediabetes. Klein and coworkers ~~*et al.*~~ recruited participants aged ≥55 years and found no increase in retinopathy prevalence with age. ~~However,~~ Herman and coworkers, however, ~~*et al.*~~ reported a higher prevalence of retinopathy in those aged ≥45 years compared to those aged 20-44 years. One study reported a higher prevalence of retinopathy (Wisconsin grade ≥15) in females (2.0%) compared to males (0.5%) [28]. Similarly, only 1 ~~one~~ study compared ethnicity-specific prevalence estimates, with higher rates reported in Hispanic White (10.0%) and non-Hispanic Black (11.6%) individuals, compared to non-Hispanic White individuals (7.5%) [7].

The highest estimated prevalence of retinopathy (14.1%) was reported in a Japanese population [26].

2.5.3 Subtype of prediabetes: Twelve studies presented prevalence estimates for IGT, with a median prevalence of 7.6% (range: 1.9-12.0%). For IFG, the median prevalence of retinopathy was 10.4% (range: 4.3-14%) based on three studies. One study defined the upper limit of IFG as <6.1 mmol/l, compared to ADA and WHO criteria (<7.0 mmol/l) [54]. Three studies reported prevalence estimates for participants with combined IFG/IGT, with a median prevalence of 8.7% (range: 0.3-9.5%). Seven studies reported prevalence estimates for retinopathy amongst participants with IFG or IGT, with a median prevalence of 6.9% (range: 1.4-14.1%).

2.5.4 Grade of retinopathy: Penman and coworkers ~~*et al.*~~ reported the prevalence of retinopathy by Early Treatment Diabetic Retinopathy Study (ETDRS) grade [43]. Of 266 participants with IGT, the number with retinopathy at ETDRS grades 15, 20 and 35 were 12 (4.5%), 9 (3.4%) and 4 (1.5%), respectively. The remaining participants (n=240, 90.2%) had retinopathy at ETDRS grade ≤14. Collins ~~et al.~~ and coworkers (n=97) found ~~reported~~ one case of proliferative retinopathy in a Samoan population, whil~~e~~st Dowse and coworkers~~*et al.*~~ (n=165) did not observe~~report~~ any cases among a mixed population of Indian, Creole and Chinese participants [11,14].

2.5.5 Comorbid ocular pathology: Van Leiden and coworkers ~~*et al.*~~ (n=165) reported a 6% prevalence of hard exudates among participants with IGT [31]. Sundling and coworkers ~~*et al.*~~ (n=38) had~~reported~~ 1 ~~one~~ participant (2.6%) with hypertensive retinopathy among those with IGT [49]. There was no difference in the prevalence of glaucoma or age-related macular degeneration in IGT compared to diabetes and NGT. Only 1 ~~one~~ study reported the incidence

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of pseudophakia (4.9%), hence the prevalence of cataract in phakic eyes could not be reliably determined [29].

2.5.6 Comorbid cardiovascular risk factors: Metabolic data from the included studies are summarised in Table S3. Six studies reported a median prevalence of 59% (range: 31-73%) for hypertension in prediabetes. Subgroup analysis was not possible owing to a lack of reporting of prevalence estimates stratified by blood pressure.

2.5.7 Method or criteria used to diagnose prediabetes: The median prevalence estimate was higher among the 15 studies that used WHO criteria (9.1%, range: 0.3-14.1%) compared to five studies that used ADA criteria (2.5%, range: 1.4-8.1%). Data on HbA1c were most commonly available (12 studies), followed by fasting plasma glucose (FPG; 9 studies) and OGTT (9 studies), as summarised in Table S2; subgroup analysis was precluded by a lack of detail on the exact test used to diagnose prediabetes. Three studies using HbA1c criteria alone for the diagnosis of prediabetes reported a median prevalence estimate of 8.1% (range: 6.6-9.7%).

2.5.8 Method used to diagnose retinopathy: All included studies diagnosed retinopathy on retinal photography, but with a range of methods, from 1-field to 7-field fundus imaging. Ten studies that used pharmacological mydriasis reported the highest median prevalence of retinopathy (9.5%, range: 1.9-13.0%), compared to 5 studies that performed non-mydriatic imaging (6.9%, range: 1.9-14.1%) and 5 studies that obtained images after dark adaptation i.e. physiological mydriasis (2.0%, range: 1.4-8.1%). The remaining studies failed to provide sufficient information on mydriasis status.

2.6 Secondary outcomes: None of the included studies found any microvascular abnormalities that were not standard features of diabetic retinopathy. Only 3 studies

reported the prevalence of maculopathy in prediabetes, based solely on retinal photography. Lamparter and coworkers *et al.* (n=922) and Pang and coworkers *et al.* (n=865) determinedreported the prevalence of clinically significant macular oedema (CSMO) as 0.2% and 2.4%, respectively [29,42]. By contrast Penman and coworkers*et al.* reported had no cases of maculopathy [43].

2.7 Post hoc analysis: Data for all study groups areis summarised in Tables S4 and S5. To explore if there is an excess prevalence of retinopathy in prediabetes compared to NGT, we performed an exploratory *post hoc* comparison. Seventeen of the 24 studies also reported prevalence estimates of retinopathy in NGT. From these studies, the median estimated prevalence of retinopathy in prediabetes (6.6%, IQR: 1.9-9.8%) was higher than in NGT (3.2%, IQR: 0.3-7.3%), summarizsed in Figure S1. Prevalence estimates and sample sizes however varied widely in NGT (0.1-10.3% and 29 to 3970 participants respectively). The majority (13/17 studies, 76%) reported a higher prevalence estimate in prediabetes than NGT.

3. DISCUSSION

3.1 Summary of retinopathy outcomes: In this systematic review, we found the median prevalence of retinopathy in prediabetes to be 7.1% (IQR: 2.4-9.7%), with the majority of studies (15/24, 62.5%) reporting a prevalence of ≥5% in prediabetes. ~~However, T~~There was, however, considerable variation in prevalence estimates (0.3-14.1%), particularly between studies that used pharmacological and physiological mydriasis. Despite this variation, on *post hoc* analysis we found a higher median prevalence of retinopathy in prediabetes (6.6%) than NGT (3.2%) within the same studies. We also found a low prevalence of more-than-mild retinopathy or CSMO in prediabetes, although data were limited.

3.2 Comparisons with previous data: A comparison of retinopathy prevalence estimates between studies was challenging given the varying definitions of dysglycaemia, retinopathy, the influence of hypertension, retinal imaging modalities, study populations and designs [39,45,50]. Clinical heterogeneity may in part explain the considerable ~~notable~~ variations in prevalence estimates. Indeed, the level of statistical heterogeneity (I^2: 93%) was also high, thus a summary estimate of pooled prevalence was not feasible. Overall, the reported excess of retinopathy in prediabetes is in keeping with other retinal and systemic microvascular changes. Microaneurysms, a well characterised DR lesion, occur in 6.9% of participants with impaired glucose metabolism [13]. Isolated retinal lesions occur in 2.6-8.6% of people without diabetes or hypertension, suggesting that dysglycaemia is an important risk factor for the development of retinal vascular changes [39]. Reported associations between prediabetes and peripheral neuropathy, nephropathy and cardiac autonomic neuropathy provide further evidence of multisystem end-organ dysfunction preceding the onset of type 2 diabetes [15,48,50].

3.3 Demographic risk factors: Risk factors for DR include age, ethnicity, disease duration, and the severity of hyperglycaemia [63]. The mean ages of participants were similar to those reported in populations with DR [63]. A paucity of age-specific retinopathy estimates limited comparisons with prior studies. Only 1 ~~one~~ study reported a higher prevalence of retinopathy in females, despite reports of retinopathy being more prevalent in males, with or without diabetes [6,41]. One study reported a higher prevalence of retinopathy among non-Hispanic Black participants, similar to data for individuals with diabetes [63].

3.4 HbA1c and comparisons between IFG and IGT: Estimates for retinopathy varied for IFG, IGT and combined IFG/IGT subgroups, but only 2 ~~two~~ studies reported data for all 3 ~~three~~ subgroups. Although people with combined IFG/IGT are at higher risk of progressing to diabetes (15-19%) compared to isolated IFG (6-9%) or IGT (4-6%), this was not reflected in the retinopathy prevalence estimates reported [50]. Despite using a narrow range of ≥5.6 and <6.1 mmol/L for IFG, Tyrberg and coworkers ~~*et al.* reported~~ found a retinopathy prevalence of 10.4% [54]. Different pathological mechanisms have been postulated in IFG and IGT, based on the origin of insulin resistance reported as predominantly hepatic and muscular, respectively [36,50]. This may explain the differences in retinopathy prevalence. HbA1c provides an indication of chronic glycaemia, whereas the OGTT measures glycaemia at a single time point. Importantly, HbA1c has a similar relationship to OGTT (fasting and 2-hour plasma glucose), as demonstrated by DETECT-2 [10]. Using HbA1c diagnostic criteria (5.7%-6.4%) alone, annual diabetes incidence rates are broadly similar in IFG and IGT (7%) [50].

3.5 Retinopathy severity: Prediabetes was predominantly associated with early stage retinopathy using ETDRS grades, and the most commonly reported retinal lesions were microaneurysms [13]. Only 2 ~~two~~ studies (n=262) reported the prevalence of proliferative diabetic retinopathy in prediabetes, with 1 ~~one~~ affected participant. Similar to diabetes, the risk

of microvascular dysfunction ~~has been reported to~~ increases with the duration of prediabetes [44].

3.6 Retinal imaging methods: Pharmacological mydriasis considerably improves the efficacy of DR screening, with a much lower poor-quality image rate than non-mydriatic fundal imaging (3.7% compared to 19.7%, respectively) [45]. In our analysis, a higher median prevalence of retinopathy was observed after pharmacological mydriasis compared to both no mydriasis and physiological mydriasis. Furthermore, studies that did not use pharmacological mydriasis were given a higher risk of bias score under the 'study instrument reliability and validity' domain. The number of retinal fields imaged also varied ~~between~~ among studies, which may have affected retinopathy estimates; however, there is an 87% agreement between two- and seven-field (gold-standard) imaging for the detection of any retinopathy [34]. Whilest seven-field imaging correlates well with clinical examination by an ophthalmologist, the technical failure rate is higher compared to two-field imaging and ungradable images affect retinopathy detection rates [46].

3.7 Comorbid ocular and metabolic disease: Data on comorbid ocular diseases were limited.; W~~w~~here reported, cataract data were presented without lens status (phakic or pseudophakic). Hypertension and other metabolic syndrome components, including dyslipidaemia and body mass index (BMI), were higher in prediabetes than NGT. Whilest the dynamic relationship between glycaemic control and retinal damage are well documented, hypertension is an important co-contributor to retinopathy [12,55,56]. Animal models and human studies suggest that retinal arteriolar endothelial dysfunction and chronic inflammation are common pathological processes underlying both DR and hypertensive retinopathy; [22,39]; h~~H~~owever, data on hypertension-specific retinopathy rates in prediabetes were limited. Dyslipidaemia in prediabetes is characterised by low high-density lipoprotein (HDL) and

raised triglycerides (TG) [8,25]. One study reported a significantly higher prevalence of metabolic syndrome in severely obese prediabetic participants compared to NGT [17]. Given the high prevalence of metabolic syndrome components in this population, it was unsurprising to note several studies reporting associations with microalbuminuria. The association between retinopathy and dyslipid~~a~~emia is more variable, with associations reported between hypercholesterolaemia and retinopathy lesions (hard exudates) and also between hypertriglyceridaemia and the risk of DR [9,33].

3.8 Limitations of the current data: Only 7~~seven~~ studies (29%) had more than 500 participants with six studies (25%) having fewer than 100 participants. Small studies are at risk of reporting bias and prevalence estimates may be less reliable. Prediabetes tests and diagnostic criteria differed between studies with prevalence data on IFG, IGT and combined subgroups from the same participants were provided in only two studies. ~~Due to~~Because of a high level of clinical heterogeneity from the variety of diagnostic approaches~~,~~ and statistical heterogeneity from variations in study design and methods, we did not perform a meta-analysis; h~~.~~ H~~h~~owever, where comparisons were made with NGT within the same study, the majority reported higher prevalence estimates in prediabetes than in NGT.

4. CONCLUSIONS

There is an increased prevalence of retinopathy in individuals with prediabetes (median: 7.1%) compared with those with normal glucose tolerance. The current glucocentric thresholds for diabetes fail to capture this burden of subclinical end-organ damage, which affects a sizeable minority of people with prediabetes. With an estimated 10% annual incidence of progression to diabetes and growing evidence of early multisystem involvement [50], greater vigilance may be needed to both monitor and mitigate end-organ damage in prediabetes.

5. METHOD OF LITERATURE SEARCH STATEMENT

5.1 Search strategy: This systematic review was registered with PROSPERO (CRD: 42020184820) and conducted using PRISMA guidelines as per a published protocol [27,47]. Comprehensive electronic literature searches were conducted in MEDLINE (via OVID), EMBASE (via OVID), Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Google Scholar and the Cochrane databases, from inception to 1 August 2020. The search strategies were independently reviewed by an expert information specialist using the Peer Review of Electronic Search Strategies (PRESS) checklist [32]. The MEDLINE search strategy is included as an example (Appendix S1). References of included studies and review articles identified during the course of the searches were used to identify any additional articles. Results from the database searches were merged using an electronic reference manager (Rayyan, Qatar Computing Research Institute, Qatar) to facilitate the removal of duplicate articles [40].

5.2 Eligibility criteria: Inclusion criteria were adults aged 18 years or older with prediabetes defined by WHO or ADA criteria [1,4]. This included IFG, IGT and combined IFG/IGT as prediabetes subgroups. Population-based cohort or cross-sectional studies from any country in any setting were considered, provided a full-text original manuscript or translation was available in English. Studies were required to report retinopathy prevalence detected on retinal photography, with or without pharmacological mydriasis, using either 1-, 2-, 3- or 7-field colour imaging. A lack of detail on the method used or quality of images taken, or a lack of reporting of the definition of prediabetes or retinopathy were noted, but not considered reasons for exclusion.

5.3 Outcomes: The primary outcome was the prevalence of any diabetes-specific retinopathy on retinal photography in prediabetes, as per International Clinical Diabetic Retinopathy Severity Scale (ICDRSS) classification [59]. This was defined by the presence of at least one of the following features on retinal photography:

(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 disease (NVD) or elsewhere (NVE)

(viii) Vitreous or pre-retinal haemorrhage

Secondary outcomes were the prevalence of: (i) any retinal microvascular abnormalities on retinal photography that are not standard features of diabetic retinopathy as per ICDRSS classification, and (ii) any maculopathy on retinal photography in prediabetes.

Where available, data on additional imaging, such as fundus fluorescein angiography (FFA) or optical coherence tomography (OCT), were extracted if reported. Data on the method of diagnosing prediabetes and cardiovascular and metabolic parameters were extracted. Metabolic syndrome was defined as per consensus criteria from the WHO, National Cholesterol Education Program Adult Treatment Panel III and ADA [1–3,37,64].

5.4 Study selection and data collection: Two reviewers independently screened titles and abstracts, excluding any that did not satisfy the eligibility criteria. Disagreements were resolved by discussion, and via third (senior) reviewer arbitration. Articles of interest were selected for

full-text assessment; if there was any doubt regarding eligibility, the full-text article was retrieved. Two reviewers independently assessed full-text articles against the eligibility criteria. A PRISMA flowchart is included in Figure 1. Two reviewers independently extracted data using pre-piloted forms. Where reported, secondary outcome data including: (i) the definition and prevalence of non-standard retinopathy features and (ii) the definition and prevalence of maculopathy features, were recorded. Prevalence estimates for co-morbid ocular pathology (e.g., cataract) and cardiovascular risk factors (e.g., hypertension, metabolic syndrome) were also recorded.

5.5 Risk of bias assessment: All eligible studies were assessed using a modified critical appraisal tool (Appendix S2). The tool features nine questions, each scoring 0 or 1, to assess selection, non-response, measurement and data analysis biases [21]. Quality assessment was conducted by two reviewers independently, with disagreements resolved by discussion. Judgments on the overall risk of bias were based on the total score for each article: 0-3 considered 'low', 4-6 considered 'moderate' and ≥7 considered 'high risk', based on the reviewers' subjective judgment of the preceding nine items [21].

5.6 Data analysis: Data were analysed using Review Manager 5 (The Cochrane Collaboration, Copenhagen, Denmark) and Microsoft Excel 2016 (Microsoft, Redmond, USA). Heterogeneity between included studies was assessed on study design, populations and methods used to measure outcomes. Statistical heterogeneity was assessed using the I^2 statistic and by visual inspection of forest plots [20]. Subgroup analyses of the primary outcome were conducted on the following covariates: (i) WHO region; (ii) age, gender, ethnicity; (iii) time since diagnosis of prediabetes; (iv) subtype of prediabetes (e.g., IGT); (v) grade of retinopathy; (vi) comorbid ocular pathology (e.g., cataract); (vii) comorbid cardiovascular risk factors (e.g., hypertension);

(viii) method or criteria used to diagnose prediabetes and (ix) method used to diagnose retinopathy.

5.7 Grading of evidence: The certainty of the evidence was assessed using the GRADE approach, detailed in Table S1 [18,24].

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The peer-reviewed protocol for this systematic review.

HIGHLIGHTS

- This systematic review found the prevalence of retinopathy in prediabetes was 7.1%.
- This represents an excess prevalence versus those with normoglycaemia.
- Hyperglycaemia can cause retinal damage prior to the diagnosis of diabetes.

CONTRIBUTION STATEMENT

All authors meet the ICMJE uniform requirements for authorship. VK, JE, UA, RAM and TLJ conceived the topic of this systematic review. VK and PN designed the search strategies, reviewed by an expert information specialist (IG), JE and SN. VK and PN performed the searches, data collection and data extraction with senior oversight from UA, JE and SN. SN provided statistical oversight of the data analysis. All authors were involved in the drafting, revision and final approval of the article to be published.

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DECLARATION OF INTEREST

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

DATA AVAILABILITY

All data generated or analysed during this study are included in this published article and its accompanying electronic supplementary material file.

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TABLE AND FIGURE LEGENDS

Table 1. Characteristics of included studies.

Footnotes: C, cohort study; **CS**, cross-sectional study; **HA**, Hispanic; **HB**, hospital-based; **IFG**, impaired fasting glucose; **IGT**, impaired glucose tolerance; **NGT**, normal glucose tolerance; **NHB**, non-Hispanic Black; **NHW**, non-Hispanic White; **nT2DM**, new or screen-detected type 2 diabetes mellitus; **PB**, population-based; **PD**, prediabetes; **T2DM**, known type 2 diabetes mellitus. * data not reported; † aggregate value including other study groups (e.g., NGT, T2DM); ‡ mean value ± 95% confidence intervals; § median value with ranges in brackets; ** prediabetes group defined by HbA1c criteria only.

Table 2. Prevalence of retinopathy in prediabetes from included studies.

Footnotes: ADA, American Diabetes Association; **CSMO**, clinically-significant macular oedema; **DRDSS**, Diabetic Retinopathy Disease Severity Scale; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **ICDRSS**, International Clinical Diabetic Retinopathy Severity Scale; **HE**, hard exudate; **IFG**, impaired fasting glucose; **IGT**, impaired glucose tolerance; **NGT**, normal glucose tolerance; **NSC**, National Screening Committee (UK); **PD**, prediabetes; **PDR**, proliferative diabetic retinopathy; **WES-DR**, Wisconsin Epidemiologic Study of Diabetic Retinopathy; **WHO**, World Health Organization. * data not reported; † additional data available for ethnicity-specific prevalence figures; ‡ IFG defined as ≥5.6 and <6.1 mmol/l; ** prediabetes group defined by HbA1c criteria only.

Figure 1. PRISMA flowchart of study selection process.

Figure 2. Forest plot of the prevalence of retinopathy in prediabetes from included studies.

Footnotes: * Prediabetes group size estimated from reported retinopathy prevalence and number of affected individuals. ** Aggregate prevalence estimates presented for impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and combined impaired fasting glucose with impaired glucose tolerance (IFG-IGT), (CI) confidence interval. All studies are population-based, except three hospital-based studies (blue highlights) and two randomised-controlled trials (green highlights). Box size proportional to precision.

Figure 3. Forest plot of the prevalence of retinopathy in prediabetes and normal glucose tolerance from included studies reporting data for both groups.

Footnotes: Normal glucose tolerance (NGT) prevalence estimates in blue, prediabetes prevalence estimates in red. [a] Prediabetes group size estimated from reported retinopathy prevalence and number of affected individuals. [b] Impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and combined impaired fasting glucose with impaired glucose tolerance (IFG/IGT) retinopathy prevalence estimates aggregated with total prediabetes group size used for 95% confidence interval (CI) estimation. [c] NGT group size estimated from the total study sample minus the reported prediabetes population. [d] Prediabetes group size estimated from reported retinopathy prevalence and number of affected individuals. All studies are population-based, except two hospital-based studies (blue highlights). Box size proportional to precision.

RESPONSE TO REVIEWERS' COMMENTS

Please find attached the final manuscript with some minor tracked changes and also a clean version. No changes have been made to the editorial revisions suggested.

Figure 1. PRISMA flowchart of study selection process

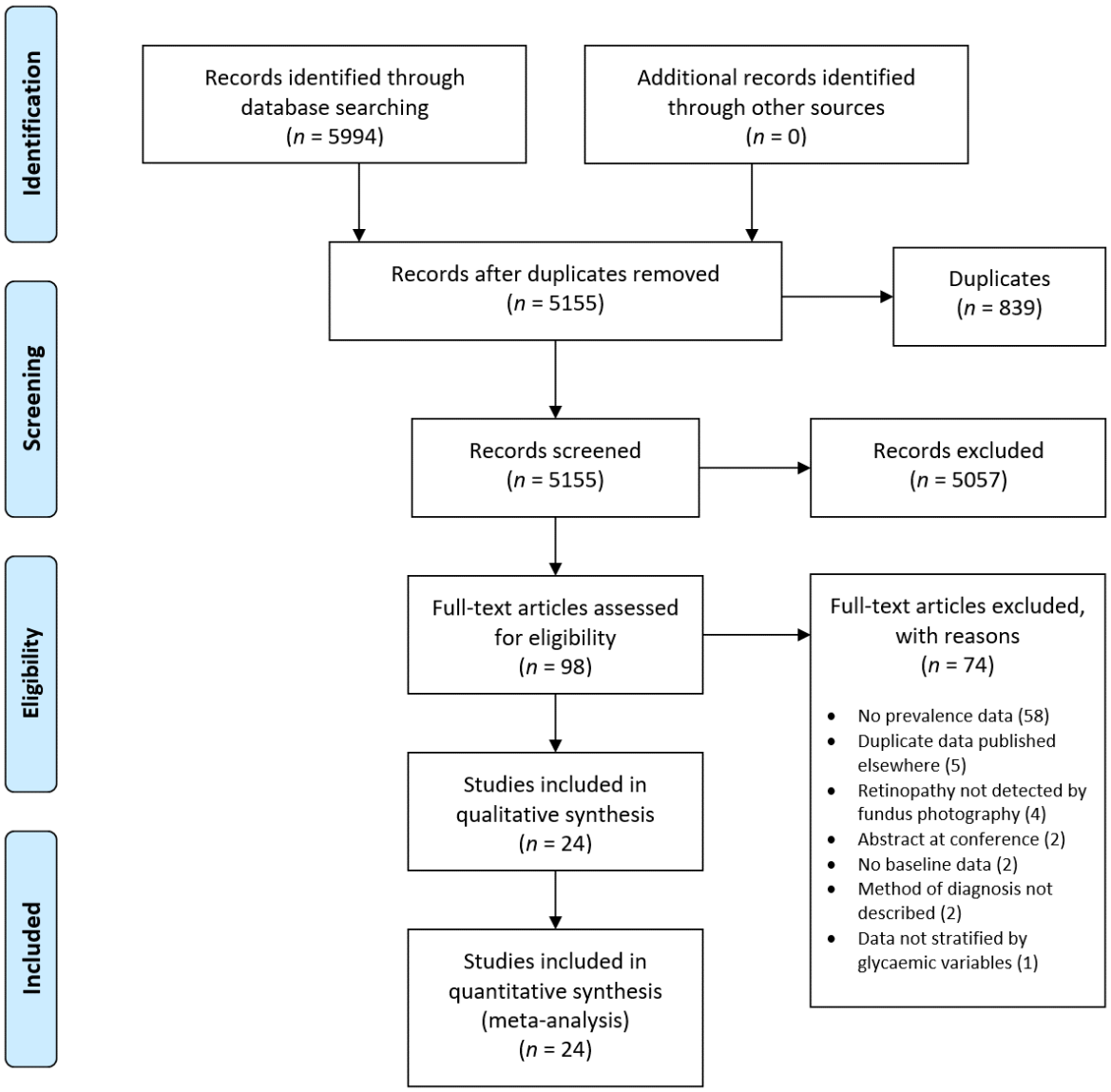
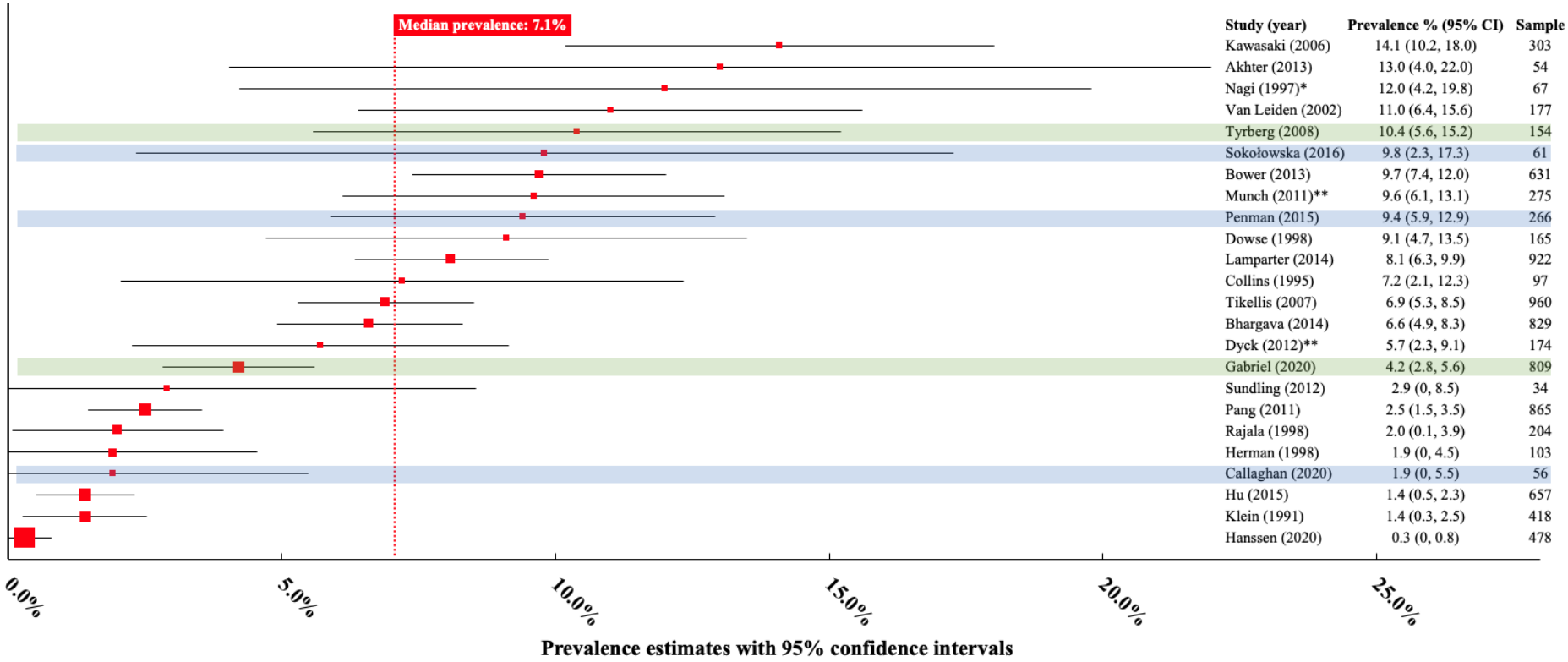
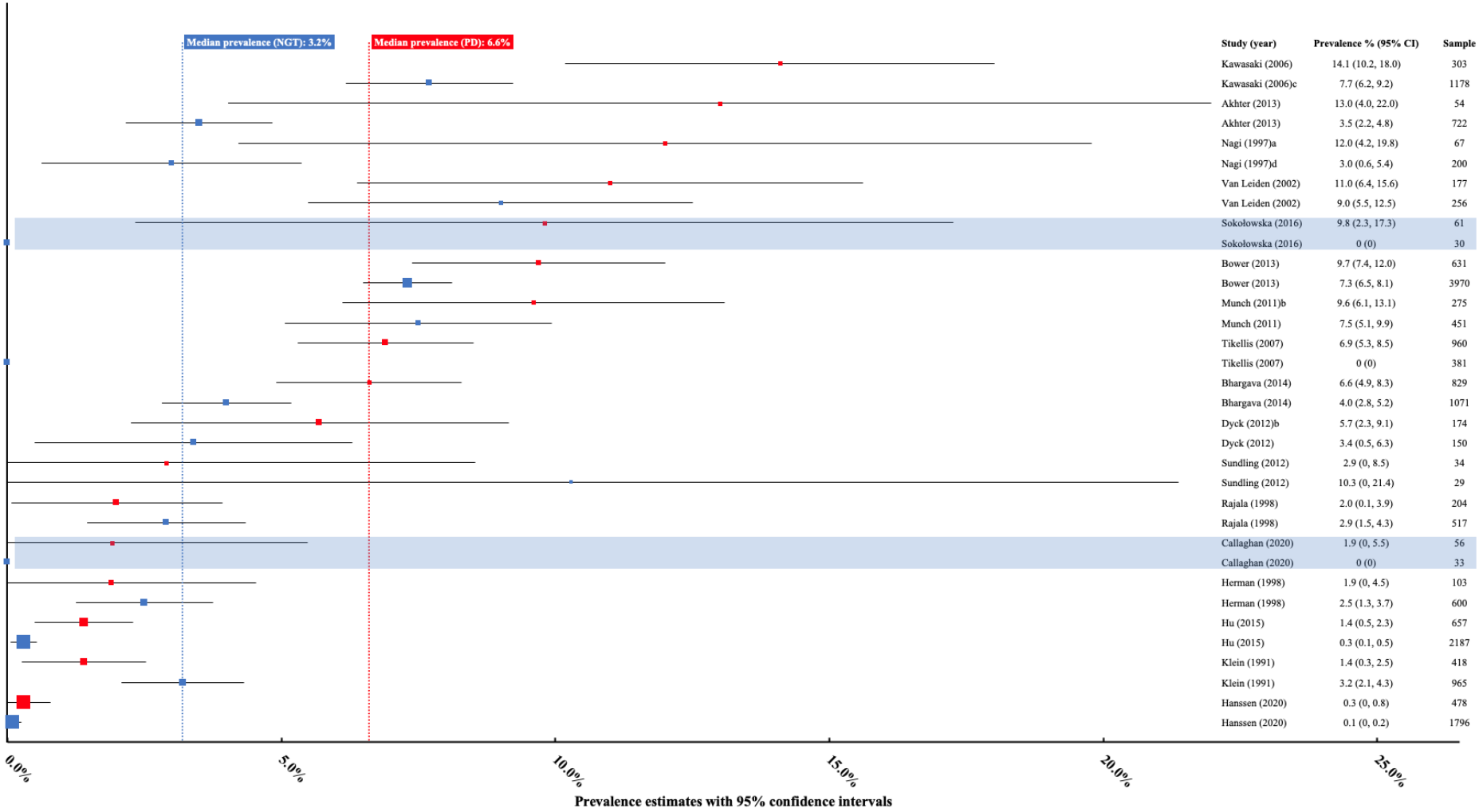


Figure 2. Forest plot of the prevalence of retinopathy in prediabetes from included studies.



Abbreviations and footnotes: * Prediabetes group size estimated from reported retinopathy prevalence and number of affected individuals. ** Aggregate prevalence estimates presented for impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and combined impaired fasting glucose with impaired glucose tolerance (IFG-IGT), (CI) confidence interval. All studies are population-based, except three hospital-based studies (blue highlights) and two randomised-controlled trials (green highlights). Box size proportional to precision.

Figure 3. Forest plot of the prevalence of retinopathy in prediabetes and normal glucose tolerance from included studies reporting data for both groups.



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1 **Table 1. Characteristics of included studies.**

Author	Country	Study period	Design	Study group(s)	Sample size	Mean age ± SD, or median age (range)	Male gender (%)	Race or ethnicity
Hanssen (2020)	The Netherlands	2010-2013	PB, C	IFG or IGT	478	61.6 ± 7.6	54	*
Callaghan (2020)	USA	2015-2018	HB, CS	IFG or IGT	56	44.7 ± 11.4	17.9	White 78.8% White 69.6% White 87.8%
Gabriel (2020)	Australia, Austria, Bulgaria, Kuwait, Poland, Serbia, Spain and Turkey	Ongoing	RCT	IFG or IGT	809	58.5 ± 7.6	41.9	*
Sokołowska (2016)	Poland	*	HB, CS	IFG or IGT	61	58	33.3	*
Penman (2015)	USA	2009-2012	HB, CS	IGT	266	65.7 ± 9.6	40.2	African American
Hu (2015)	China	2006-	PB, CS	IFG or IGT	657	45.6 ± 1.3 ‡	35.0	Chinese
Bhargava (2014)	Singapore	*	PB, CS	PD**	829	*	*	Indian
Lamparter (2014)	Germany	2007-2008	PB, C	PD**	922	59.9 ± 9.1	51.8	*
Akhter (2013)	Bangladesh	*	PB, CS	IFG or IGT	54	*	56 †	Bangladeshi
Bower (2013)	USA	2005-2008	PB, CS	PD**	631	*	*	NHW: 41% NHB: 30% HA: 29%

Dyck (2012)	USA	2000-2005	PB, CS	IFG IGT IFG with IGT	174	64 (22-76) [§]	67.8	*
Sundling (2012)	Norway	2004-2005	PB, CS	IGT	34	57 ± 15	36.8	*
Pang (2011)	China	1996-2007	PB, CS	IGT	865	62.3 ± 10.8	42.9	Chinese
Munch (2011)	Denmark	1991-2001	PB, CS	IFG IGT IFG with IGT	59 152 64	*	*	*
Tyrberg (2008)	Sweden	*	RCT	IFG	154	*	58.4	*
Tikellis (2007)	Australia	1999-2000	PB, CS	IFG or IGT	960	58.9 ±13.5	43.0	*
Kawasaki (2006)	Japan	2000-2002	PB, CS	IGT	303 [†]	58.6 [†]	42.3 [†]	Japanese
Van Leiden (2002)	The Netherlands	1989-1992	PB, CS	IGT	177	64.2 ± 7.3	51	Caucasian
Herman (1998)	Egypt	*	PB, CS	IGT	103	*	41	*
Rajala (1998)	Finland	1990-1992	PB, CS	IGT	204	*	43.9 [†]	*
Dowse (1998)	Mauritius	1987-1992	PB, CS	IGT	165	*	45.2 [†]	Indian, Creole and Chinese

Nagi (1997)	USA	1982-1990	PB, CS	IGT	288 (incl. NGT) †	45 (15-93, incl. NGT) †§	51.0 (incl. NGT) †	Pima Indians
Collins (1995)	Samoa	1978-1991	PB, CS	IGT	97	*	37.2	Samoan
Klein (1991)	USA	1984-1987	PB, CS	IGT	418	*	39.0	White

Footnotes: C, cohort study; **CS**, cross-sectional study; **HA**, Hispanic; **HB**, hospital-based; **IFG**, impaired fasting glucose; **IGT**, impaired glucose tolerance; **NGT**, normal glucose tolerance; **NHB**, non-Hispanic Black; **NHW**, non-Hispanic White; **nT2DM**, new or screen-detected type 2 diabetes mellitus; **PB**, population-based; **PD**, prediabetes; **T2DM**, known type 2 diabetes mellitus. * data not reported; † aggregate value including other study groups (e.g., NGT, T2DM); ‡ mean value ± 95% confidence intervals; § median value with ranges in brackets; ** prediabetes group defined by HbA1c criteria only.

1 **Table 2. Prevalence of retinopathy in prediabetes from included studies.**

Author	Definition of retinopathy	Photographic method for diagnosis of retinopathy	Definition of prediabetes	Study group(s)	Participants with retinopathy, *n*	Sample size	Prevalence estimates (%)	Additional outcome data
Hanssen (2020)	ETDRS and ICDRSS	Colour digital	WHO	IFG or IGT	*	478	0.3	*
Callaghan (2020)	*	Non-mydriatic colour digital	ADA	IFG or IGT	*	56	1.9	*
Gabriel (2020)	ETDRS ≥14	Mydriatic, 3-field colour digital	WHO	IFG or IGT	34	809	4.2	*
Sokołowska (2016)	*	Colour digital	*	IFG or IGT	6	61	9.8	*
Penman (2015)	ETDRS ≥14	Mydriatic, 7-field colour digital	WHO	IGT	25	266	9.4	CSMO: 0% CSMO: 7.8%
Hu (2015)	ETDRS	Dark-adapted, 1-field, 45-degree colour digital	ADA	IFG or IGT	9	657	1.4	*
Bhargava (2014)	ETDRS >14	Mydriatic, 2-field, 45-degree colour digital	ADA	PD**	55	829	6.6	*
Lamparter (2014)	ETDRS	Dark-adapted, 2-field colour digital	ADA	PD**	75	922	8.1	CSMO: 0.2%
Akhter (2013)	ETDRS	Mydriatic, 3-field colour digital	WHO	IFG or IGT	7	54	13	*

Bower (2013)	ETDRS ≥14	Non-mydriatic, 2-field, 45-degree colour digital	WHO	PD**	*	631	9.7 †	*
Dyck (2012)	NSC: R0-R3	7-field colour digital	ADA and WHO	IFG IGT IFG with IGT	*	118 19 37	4.3 9.9 8.7	WHO cut-off for IFG (6.1 mmol/L) but also included abnormal A1c as per ADA
Sundling (2012)	DRDSS: 5 stages	Non-mydriatic, 1-field, 45-degree colour digital	WHO	IGT	1	34	2.9	*
Pang (2011)	DRDSS: G1-4	Dark-adapted, 1-field, 45-degree colour digital	ADA	IGT	22	865	2.5	CSMO: 2.4%
Munch (2011)	ETDRS ≥15	Mydriatic, 7-field, 60-degree colour digital	WHO	IFG IGT IFG with IGT	*	59 152 64	14 8 9.5	*
Tyrberg (2008)	Alternative WES-DR ≥21	Mydriatic, 2-field, colour film	Non-standard ‡	IFG	16	154	10.4	*
Tikellis (2007)	Wisconsin	Non-mydriatic, 2-field, 45-degree colour digital	WHO	IFG or IGT	66	960	6.9	*
Kawasaki (2006)	Not defined: any MA, Hg or exudate	Non-mydriatic, 1-field, 45-degree colour digital	WHO	IFG or IGT	*	303	14.1	*
Van Leiden (2002)	EURODIAB: ≥1 MA, Hg or hard exudate	Mydriatic, 2-field colour digital	WHO	IGT	*	177	11	HE: 6%
Herman (1998)	Wisconsin	Mydriatic digital	WHO	IGT	*	103	1.9	*
Rajala (1998)	University Hospital of Oulu classification: G1-4	Dark-adapted, 1-field, 45-degree film	WHO (*1985*)	IGT	*	204	2.0	*

Dowse (1998)	Airlie-House	3-field, 45-degree digital	WHO	IGT	15	165	9.1	PDR: 0%
Nagi (1997)	Modified Airlie-House	Mydriatic, 2-field, 45-degree digital	WHO	IGT	8	288 (incl. NGT)	12.0	*
Collins (1995)	Airlie-House	Mydriatic, 3-field, 45-degree	WHO	IGT	7	97	7.2	PDR: 1.0%
Klein (1991)	Wisconsin ≥15	Dark-adapted, 1-field, 45-degree	WHO	IGT	6	418	1.4	*

Footnotes: ADA, American Diabetes Association; **CSMO**, clinically-significant macular oedema; **DRDSS**, Diabetic Retinopathy Disease Severity Scale; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **ICDRSS**, International Clinical Diabetic Retinopathy Severity Scale; **HE**, hard exudate; **IFG**, impaired fasting glucose; **IGT**, impaired glucose tolerance; **NGT**, normal glucose tolerance; **NSC**, National Screening Committee (UK); **PD**, prediabetes; **PDR**, proliferative diabetic retinopathy; **WES-DR**, Wisconsin Epidemiologic Study of Diabetic Retinopathy; **WHO**, World Health Organization. * data not reported; † additional data available for ethnicity-specific prevalence figures; ‡ IFG defined as ≥5.6 and <6.1 mmol/l; ** prediabetes group defined by HbA1c criteria only.

Table 3. Prevalence of retinopathy in prediabetes from included studies.

Author	Definition of retinopathy	Photographic method for diagnosis of retinopathy	Definition of prediabetes	Study group(s)	Participants with retinopathy, *n*	Sample size	Prevalence estimates (%)	Additional outcome data
Hanssen (2020)	ETDRS and ICDRSS	Colour digital	WHO	IFG or IGT	*	478	0.3	*
Callaghan (2020)	*	Non-mydriatic colour digital	ADA	IFG or IGT	*	56	1.9	*
Gabriel (2020)	ETDRS ≥14	Mydriatic, 3-field colour digital	WHO	IFG or IGT	34	809	4.2	*
Sokołowska (2016)	*	Colour digital	*	IFG or IGT	6	61	9.8	*
Penman (2015)	ETDRS ≥14	Mydriatic, 7-field colour digital	WHO	IGT	25	266	9.4	CSMO: 0% CSMO: 7.8%
Hu (2015)	ETDRS	Dark-adapted, 1-field, 45-degree colour digital	ADA	IFG or IGT	9	657	1.4	*
Bhargava (2014)	ETDRS >14	Mydriatic, 2-field, 45-degree colour digital	ADA	PD**	55	829	6.6	*
Lamparter (2014)	ETDRS	Dark-adapted, 2-field colour digital	ADA	PD**	75	922	8.1	CSMO: 0.2%
Akhter (2013)	ETDRS	Mydriatic, 3-field colour digital	WHO	IFG or IGT	7	54	13	*

Bower (2013)	ETDRS ≥14	Non-mydriatic, 2-field, 45-degree colour digital	WHO	PD**	*	631	9.7 †	*
Dyck (2012)	NSC: R0-R3	7-field colour digital	ADA and WHO	IFG IGT IFG with IGT	*	118 19 37	4.3 9.9 8.7	WHO cut-off for IFG (6.1 mmol/L) but also included abnormal A1c as per ADA
Sundling (2012)	DRDSS: 5 stages	Non-mydriatic, 1-field, 45-degree colour digital	WHO	IGT	1	34	2.9	*
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5. STATEMENT OF DISCLOSURE

Each author must complete a statement of disclosure.

Manuscript Title:	**The prevalence of retinopathy in prediabetes: a systematic review**
Authors:	Varo Kirthi, Paul Nderitu, Uazman Alam, Jennifer Evans, Sarah Nevitt, Rayaz A. Malik, David Hopkins, Timothy L. Jackson

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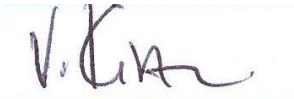
Varo Kirthi



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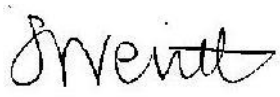

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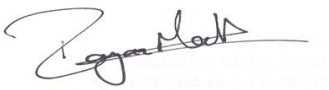

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TITLE

The prevalence of retinopathy in prediabetes: A systematic review

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KEY WORDS

Prediabetes, impaired fasting glucose, impaired glucose tolerance, retinopathy, prevalence, epidemiology

ABSTRACT

Diabetic retinopathy is a leading cause of vision loss globally. The current diagnostic thresholds for diabetes are still based on historic data correlating glycaemic parameters with retinopathy; however, an excess prevalence of retinopathy has also been reported in prediabetes. We aimed to determine the reported prevalence of retinopathy in adults with prediabetes. We performed searches using MEDLINE, EMBASE, PubMed, Web of Science, CINAHL, Google Scholar and the Cochrane databases from inception to 1 August 2020. We evaluated methodological quality and certainty of the evidence using a validated risk of bias tool and GRADE, respectively. Twenty-four studies (8759 participants with prediabetes) were included after screening 5994 abstracts and reviewing 98 full-text records. Nineteen studies (79%) reported population-based data. Retinopathy prevalence estimates ranged between 0.3-14.1% (median 7.1%, interquartile range 2.4-10.0%), with high variance in estimates due to differing screening methods, retinopathy grading protocols and study populations. We judged this as low-certainty evidence using GRADE, downgrading for risk of bias and inconsistency. From studies that compared both populations, *post hoc* analysis revealed a lower median retinopathy prevalence in normal glucose tolerance (3.2%, interquartile range 0.3-7.3%) than prediabetes (6.6%, interquartile range 1.9-9.8%). These data suggest an excess prevalence of retinopathy in prediabetes.

1. INTRODUCTION

Prediabetes is defined as suboptimal glycemia that does not reach the threshold for type 2 diabetes [1,4]. Worldwide, approximately one in 13 adults (374 million) aged 20-79 years have prediabetes, and the vast majority are unaware of the diagnosis [23]. There is a significant predicted burden, with the International Diabetes Federation projecting 587 million people (8.3% of adults) to have prediabetes by 2045 [23].

The World Health Organization (WHO) uses two specific parameters to define prediabetes: (i) impaired fasting glucose (IFG), defined as a fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110-125 mg/dL) and (ii) impaired glucose tolerance (IGT), defined as a two-hour plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dL) after ingestion of 75g oral glucose, or a combination of the two based on a two-hour oral glucose tolerance test (OGTT) [1]. The American Diabetes Association (ADA) uses the same cut-off value for IGT (140-200 mg/dL), but has a lower cut-off value for IFG (100-125 mg/dL) [4]. In addition, the ADA includes a haemoglobin A1c (HbA1c) level of 5.7-6.4% to define prediabetes [4].

Current diagnostic thresholds for fasting and two-hour post-load plasma glucose levels are based on the presence of retinopathy reported in population-based studies in Pima Indians, Egypt, and the United States; [53] however, subsequent studies have failed to confirm these thresholds, attributed to broad definitions of retinopathy and limited statistical power [52,61]. The DETECT-2 study showed that diabetic retinopathy (DR) was associated with a fasting plasma glucose of 6.5 mmol/l [10]. Data also suggest that end-organ complications occur prior to the onset of type 2 diabetes [50]. Compared to individuals with normal glucose tolerance (NGT), those with prediabetes have an increased prevalence of microvascular disease, elevated all-cause mortality, and a doubling of coronary heart disease mortality [51,57]. People with

prediabetes and concomitant microvascular disease are also more likely to develop type 2 diabetes [5,30,58].

In people with diabetes, the worldwide prevalence of any DR, proliferative DR, diabetic macular edema and vision-threatening DR is 34.6%, 7.0%, 6.8% and 10.2%, respectively [63]. Hence the early diagnosis of sight-threatening disease is key [38,50]. Although approaches to population-based screening vary by country, digital retinal photography is considered the most effective screening method for DR [62]. Although isolated retinopathy occurs with increasing age and hypertension, the prevalence varies between 2.6-8.6% even in individuals without diabetes or hypertension, which may be attributed to prediabetes [39,60]. We aimed to determine and discuss the prevalence of retinopathy in prediabetes by undertaking a systematic review of published data, using evidence-based Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2. RESULTS

2.1 Study characteristics: After removal of duplicate entries, we identified 5155 records from the electronic database searches and selected 98 records for full-text review. Of these, 24 studies (8759 participants with prediabetes) were included in the final review. Reasons for exclusion after full-text review are shown in Figure 1.

Characteristics of the included studies are presented in Table 1. Of the 15 studies that reported age data, 11 reported a mean or median age of participants. Among the 21 studies that reported gender data, gender ratios varied widely from 17.9% to 67.8% male.

Studies were conducted in 22 different countries and 6 WHO regions. Eight studies were conducted in Europe, 6 in the Americas (USA), six in the Western Pacific (China, Japan, Singapore, Australia and Samoa), and 1 each in South-East Asia (Bangladesh), Africa (Mauritius) and the Eastern Mediterranean (Egypt). One publication was a multinational study conducted across 9 countries [16]. Thirteen studies reported race or ethnicity data, from a wide variety of backgrounds; 2 studies exclusively examined African Americans and Pima Indians, both from the USA [35,43]. The majority of studies were cross-sectional and population-based (19/24, 79%); three were cross-sectional, hospital-based studies and two were double-blind, randomised-controlled trials reporting baseline prevalence data. Sample sizes for the included studies varied between 34 and 960. Fifteen studies used WHO criteria to define prediabetes, five used ADA criteria, two used non-standard or superseded WHO criteria, 1failed to report how prediabetes was defined, and 1study used stricter non-standard IFG criteria [54].

2.2 Risk of bias assessment: Points scored on individual risk of bias items and the overall scores of the included studies are provided in Table S1. We deemed the majority of studies (19/24, 79%) ‘low’ risk whilst the remaining five were deemed ‘moderate’ risk. The most

common issues were: (i) the likelihood of non-response bias due to a response rate <75% (17 studies); (ii) the study instrument not shown to have reliability or validity, scored for any study that failed to perform pharmacological mydriasis (14 studies) and (iii) a lack of census or some form of random selection performed to select the sample (9 studies).

Owing to variations in study populations, fields captured on retinal photography, retinopathy classifications, use of pharmacological dilation and diagnostic methods for prediabetes, we considered clinical and statistical (I^2: 93%) heterogeneity too high to perform a meta-analysis [20]. Where quantitative data were available, we recorded median estimates and ranges. Where such data were lacking, we conducted a narrative analysis of the data.

2.3 Primary outcome: A summary of the prevalence data is shown in Figure 2 and Table 2. The median estimated prevalence of retinopathy in prediabetes was 7.1% (interquartile range (IQR): 2.4-9.7%); however, prevalence estimates varied widely, from 0.3% in a study from the Netherlands (n=478) to 14.1% in a study from Japan (n=303) [19,26]. The median sample size for the at-risk population with prediabetes was 235 (range 34-960).

2.4 GRADE assessment of primary outcome: Confidence in the body of evidence for the primary outcome was assessed using the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) domains: (i) risk of bias, (ii) inconsistency, (iii) imprecision, (iv) indirectness and (v) publication bias, summarised in Table S2. Although the overall risk of bias in most studies was low, the majority of studies were at risk of non-response bias and a significant proportion reported non-random sampling methods. There was also evidence of inconsistency due to a wide variation in prevalence estimates, which did not correlate with study settings. Although 95% confidence intervals for most prevalence estimates were wide, given the total number of participants, if data were pooled the overall estimate of

prevalence may be reasonably precise. As the majority of studies were population-based and all studies measured the outcome of interest, we found no evidence of indirectness. Although studies of varying sample sizes reported high and low prevalence estimates, we found no evidence of publication bias. We deemed the overall GRADE assessment of the prevalence of retinopathy in prediabetes low certainty, downgrading one level for risk of bias and one level for inconsistency.

2.5 Subgroup analyses of primary outcome: Where quantitative subgroup data were lacking, we conducted a narrative analysis. As insufficient data were reported, we did not perform an analysis of the time since diagnosis of prediabetes on the prevalence of retinopathy.

2.5.1 WHO region: Median retinopathy estimates by WHO region were 7.6% (range: 1.4-12.0%) for the Americas, 8.9% (range: 0.3-11.0%) for Europe and 6.8% (range: 1.4-14.1%) for the Western Pacific. Only 1 study contributed to the retinopathy estimates for Africa (9.1%), South-East Asia (13.0%), and the Eastern Mediterranean (1.9%).

2.5.2 Age, gender and ethnicity: Two studies reported age-specific prevalence estimates in prediabetes. Klein and coworkers recruited participants aged ≥55 years and found no increase in retinopathy prevalence with age. Herman and coworkers, however, reported a higher prevalence of retinopathy in those aged ≥45 years compared to those aged 20-44 years. One study reported a higher prevalence of retinopathy (Wisconsin grade ≥15) in females (2.0%) compared to males (0.5%) [28]. Similarly, only 1 study compared ethnicity-specific prevalence estimates, with higher rates reported in Hispanic White (10.0%) and non-Hispanic Black (11.6%) individuals, compared to non-Hispanic White individuals (7.5%) [7]. The highest estimated prevalence of retinopathy (14.1%) was reported in a Japanese population [26].

2.5.3 Subtype of prediabetes: Twelve studies presented prevalence estimates for IGT, with a median prevalence of 7.6% (range: 1.9-12.0%). For IFG, the median prevalence of retinopathy was 10.4% (range: 4.3-14%) based on three studies. One study defined the upper limit of IFG as <6.1 mmol/l, compared to ADA and WHO criteria (<7.0 mmol/l) [54]. Three studies reported prevalence estimates for participants with combined IFG/IGT, with a median prevalence of 8.7% (range: 0.3-9.5%). Seven studies reported prevalence estimates for retinopathy amongst participants with IFG or IGT, with a median prevalence of 6.9% (range: 1.4-14.1%).

2.5.4 Grade of retinopathy: Penman and coworkers reported the prevalence of retinopathy by Early Treatment Diabetic Retinopathy Study (ETDRS) grade [43]. Of 266 participants with IGT, the number with retinopathy at ETDRS grades 15, 20 and 35 were 12 (4.5%), 9 (3.4%) and 4 (1.5%), respectively. The remaining participants (n=240, 90.2%) had retinopathy at ETDRS grade ≤14. Collins and coworkers (n=97) found one case of proliferative retinopathy in a Samoan population, while Dowse and coworkers (n=165) did not observe any cases among a mixed population of Indian, Creole and Chinese participants [11,14].

2.5.5 Comorbid ocular pathology: Van Leiden and coworkers (n=165) reported a 6% prevalence of hard exudates among participants with IGT [31]. Sundling and coworkers (n=38) had 1 participant (2.6%) with hypertensive retinopathy among those with IGT [49]. There was no difference in the prevalence of glaucoma or age-related macular degeneration in IGT compared to diabetes and NGT. Only 1 study reported the incidence of pseudophakia (4.9%), hence the prevalence of cataract in phakic eyes could not be reliably determined [29].

2.5.6 Comorbid cardiovascular risk factors: Metabolic data from the included studies are summariszd in Table S3. Six studies reported a median prevalence of 59% (range: 31-73%) for

hypertension in prediabetes. Subgroup analysis was not possible owing to a lack of reporting of prevalence estimates stratified by blood pressure.

2.5.7 Method or criteria used to diagnose prediabetes: The median prevalence estimate was higher among the 15 studies that used WHO criteria (9.1%, range: 0.3-14.1%) compared to five studies that used ADA criteria (2.5%, range: 1.4-8.1%). Data on HbA1c were most commonly available (12 studies), followed by fasting plasma glucose (FPG; 9 studies) and OGTT (9 studies), as summarised in Table S2; subgroup analysis was precluded by a lack of detail on the exact test used to diagnose prediabetes. Three studies using HbA1c criteria alone for the diagnosis of prediabetes reported a median prevalence estimate of 8.1% (range: 6.6-9.7%).

2.5.8 Method used to diagnose retinopathy: All included studies diagnosed retinopathy on retinal photography, but with a range of methods, from 1-field to 7-field fundus imaging. Ten studies that used pharmacological mydriasis reported the highest median prevalence of retinopathy (9.5%, range: 1.9-13.0%), compared to 5 studies that performed non-mydriatic imaging (6.9%, range: 1.9-14.1%) and 5 studies that obtained images after dark adaptation i.e. physiological mydriasis (2.0%, range: 1.4-8.1%). The remaining studies failed to provide sufficient information on mydriasis status.

2.6 Secondary outcomes: None of the included studies found any microvascular abnormalities that were not standard features of diabetic retinopathy. Only 3 studies reported the prevalence of maculopathy in prediabetes, based solely on retinal photography. Lamparter and coworkers (n=922) and Pang and coworkers (n=865) determined the prevalence of clinically significant macular edema (CSMO) as 0.2% and 2.4%, respectively [29,42]. By contrast Penman and coworkers had no cases of maculopathy [43].

2.7 Post hoc analysis: Data for all study groups are summarised in Tables S4 and S5. To explore if there is an excess prevalence of retinopathy in prediabetes compared to NGT, we performed an exploratory *post hoc* comparison. Seventeen of the 24 studies also reported prevalence estimates of retinopathy in NGT. From these studies, the median estimated prevalence of retinopathy in prediabetes (6.6%, IQR: 1.9-9.8%) was higher than in NGT (3.2%, IQR: 0.3-7.3%), summarized in Figure S1. Prevalence estimates and sample sizes however varied widely in NGT (0.1-10.3% and 29 to 3970 participants respectively). The majority (13/17 studies, 76%) reported a higher prevalence estimate in prediabetes than NGT.

3. DISCUSSION

3.1 Summary of retinopathy outcomes: In this systematic review, we found the median prevalence of retinopathy in prediabetes to be 7.1% (IQR: 2.4-9.7%), with the majority of studies (15/24, 62.5%) reporting a prevalence of ≥5% in prediabetes. There was, however, considerable variation in prevalence estimates (0.3-14.1%), particularly between studies that used pharmacological and physiological mydriasis. Despite this variation, on *post hoc* analysis we found a higher median prevalence of retinopathy in prediabetes (6.6%) than NGT (3.2%) within the same studies. We also found a low prevalence of more-than-mild retinopathy or CSMO in prediabetes, although data were limited.

3.2 Comparisons with previous data: A comparison of retinopathy prevalence estimates between studies was challenging given the varying definitions of dysglycaemia, retinopathy, the influence of hypertension, retinal imaging modalities, study populations and designs [39,45,50]. Clinical heterogeneity may in part explain the considerable variations in prevalence estimates. Indeed, the level of statistical heterogeneity (I^2: 93%) was also high, thus a summary estimate of pooled prevalence was not feasible. Overall, the reported excess of retinopathy in prediabetes is in keeping with other retinal and systemic microvascular changes. Microaneurysms, a well characterised DR lesion, occur in 6.9% of participants with impaired glucose metabolism [13]. Isolated retinal lesions occur in 2.6-8.6% of people without diabetes or hypertension, suggesting that dysglycaemia is an important risk factor for the development of retinal vascular changes [39]. Reported associations between prediabetes and peripheral neuropathy, nephropathy and cardiac autonomic neuropathy provide further evidence of multisystem end-organ dysfunction preceding the onset of type 2 diabetes [15,48,50].

3.3 Demographic risk factors: Risk factors for DR include age, ethnicity, disease duration, and the severity of hyperglycemia [63]. The mean ages of participants were similar to those reported in populations with DR [63]. A paucity of age-specific retinopathy estimates limited comparisons with prior studies. Only 1study reported a higher prevalence of retinopathy in females, despite reports of retinopathy being more prevalent in males, with or without diabetes [6,41]. One study reported a higher prevalence of retinopathy among non-Hispanic Black participants, similar to data for individuals with diabetes [63].

3.4 HbA1c and comparisons between IFG and IGT: Estimates for retinopathy varied for IFG, IGT and combined IFG/IGT subgroups, but only 2studies reported data for all 3subgroups. Although people with combined IFG/IGT are at higher risk of progressing to diabetes (15-19%) compared to isolated IFG (6-9%) or IGT (4-6%), this was not reflected in the retinopathy prevalence estimates reported [50]. Despite using a narrow range of ≥5.6 and <6.1 mmol/L for IFG, Tyrberg and coworkers found a retinopathy prevalence of 10.4% [54]. Different pathological mechanisms have been postulated in IFG and IGT, based on the origin of insulin resistance reported as predominantly hepatic and muscular, respectively [36,50]. This may explain the differences in retinopathy prevalence. HbA1c provides an indication of chronic glycaemia, whereas the OGTT measures glycemia at a single time point. Importantly, HbA1c has a similar relationship to OGTT (fasting and 2-hour plasma glucose), as demonstrated by DETECT-2 [10]. Using HbA1c diagnostic criteria (5.7%-6.4%) alone, annual diabetes incidence rates are broadly similar in IFG and IGT (7%) [50].

3.5 Retinopathy severity: Prediabetes was predominantly associated with early stage retinopathy using ETDRS grades, and the most commonly reported retinal lesions were microaneurysms [13]. Only 2 studies (n=262) reported the prevalence of proliferative diabetic

retinopathy in prediabetes, with 1affected participant. Similar to diabetes, the risk of microvascular dysfunction increases with the duration of prediabetes [44].

3.6 Retinal imaging methods: Pharmacological mydriasis considerably improves the efficacy of DR screening, with a much lower poor-quality image rate than non-mydriatic fundal imaging (3.7% compared to 19.7%, respectively) [45]. In our analysis a higher median prevalence of retinopathy was observed after pharmacological mydriasis compared to both no mydriasis and physiological mydriasis. Furthermore, studies that did not use pharmacological mydriasis were given a higher risk of bias score under the 'study instrument reliability and validity' domain. The number of retinal fields imaged also varied among studies, which may have affected retinopathy estimates; however, there is an 87% agreement between two- and seven-field (gold-standard) imaging for the detection of any retinopathy [34]. While seven-field imaging correlates well with clinical examination by an ophthalmologist, the technical failure rate is higher compared to two-field imaging and ungradable images affect retinopathy detection rates [46].

3.7 Comorbid ocular and metabolic disease: Data on comorbid ocular diseases were limited. Where reported, cataract data were presented without lens status (phakic or pseudophakic). Hypertension and other metabolic syndrome components, including dyslipidaemia and body mass index (BMI), were higher in prediabetes than NGT. While the dynamic relationship between glycemic control and retinal damage are well documented, hypertension is an important cocontributor to retinopathy [12,55,56]. Animal models and human studies suggest that retinal arteriolar endothelial dysfunction and chronic inflammation are common pathological processes underlying both DR and hypertensive retinopathy [22,39]; however, data on hypertension-specific retinopathy rates in prediabetes were limited. Dyslipidaemia in prediabetes is characterised by low high-density lipoprotein (HDL) and raised triglycerides

(TG) [8,25]. One study reported a significantly higher prevalence of metabolic syndrome in severely obese prediabetic participants compared to NGT [17]. Given the high prevalence of metabolic syndrome components in this population, it was unsurprising to note several studies reporting associations with microalbuminuria. The association between retinopathy and dyslipidemia is more variable, with associations reported between hypercholesterolaemia and retinopathy lesions (hard exudates) and also between hypertriglyceridaemia and the risk of DR [9,33].

3.8 Limitations of the current data: Only 7 studies (29%) had more than 500 participants with six studies (25%) having fewer than 100 participants. Small studies are at risk of reporting bias and prevalence estimates may be less reliable. Prediabetes tests and diagnostic criteria differed between studies with prevalence data on IFG, IGT and combined subgroups from the same participants were provided in only two studies. Because of a high level of clinical heterogeneity from the variety of diagnostic approaches and statistical heterogeneity from variations in study design and methods, we did not perform a meta-analysis; however, where comparisons were made with NGT within the same study, the majority reported higher prevalence estimates in prediabetes than in NGT.

4. CONCLUSIONS

There is an increased prevalence of retinopathy in individuals with prediabetes (median: 7.1%) compared with those with normal glucose tolerance. The current glucocentric thresholds for diabetes fail to capture this burden of subclinical end-organ damage, which affects a sizeable minority of people with prediabetes. With an estimated 10% annual incidence of progression to diabetes and growing evidence of early multisystem involvement [50], greater vigilance may be needed to both monitor and mitigate end-organ damage in prediabetes.

5. METHOD OF LITERATURE SEARCH STATEMENT

5.1 Search strategy: This systematic review was registered with PROSPERO (CRD: 42020184820) and conducted using PRISMA guidelines as per a published protocol [27,47]. Comprehensive electronic literature searches were conducted in MEDLINE (via OVID), EMBASE (via OVID), Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Google Scholar and the Cochrane databases, from inception to 1 August 2020. The search strategies were independently reviewed by an expert information specialist using the Peer Review of Electronic Search Strategies (PRESS) checklist [32]. The MEDLINE search strategy is included as an example (Appendix S1). References of included studies and review articles identified during the course of the searches were used to identify any additional articles. Results from the database searches were merged using an electronic reference manager (Rayyan, Qatar Computing Research Institute, Qatar) to facilitate the removal of duplicate articles [40].

5.2 Eligibility criteria: Inclusion criteria were adults aged 18 years or older with prediabetes defined by WHO or ADA criteria [1,4]. This included IFG, IGT and combined IFG/IGT as prediabetes subgroups. Population-based cohort or cross-sectional studies from any country in any setting were considered, provided a full-text original manuscript or translation was available in English. Studies were required to report retinopathy prevalence detected on retinal photography, with or without pharmacological mydriasis, using either 1-, 2-, 3- or 7-field colour imaging. A lack of detail on the method used or quality of images taken, or a lack of reporting of the definition of prediabetes or retinopathy were noted, but not considered reasons for exclusion.

5.3 Outcomes: The primary outcome was the prevalence of any diabetes-specific retinopathy on retinal photography in prediabetes, as per International Clinical Diabetic Retinopathy Severity Scale (ICDRSS) classification [59]. This was defined by the presence of at least one of the following features on retinal photography:

(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 disease (NVD) or elsewhere (NVE)
(viii) Vitreous or pre-retinal haemorrhage

Secondary outcomes were the prevalence of: (i) any retinal microvascular abnormalities on retinal photography that are not standard features of diabetic retinopathy as per ICDRSS classification, and (ii) any maculopathy on retinal photography in prediabetes.

Where available, data on additional imaging, such as fundus fluorescein angiography (FFA) or optical coherence tomography (OCT), were extracted if reported. Data on the method of diagnosing prediabetes and cardiovascular and metabolic parameters were extracted. Metabolic syndrome was defined as per consensus criteria from the WHO, National Cholesterol Education Program Adult Treatment Panel III and ADA [1–3,37,64].

5.4 Study selection and data collection: Two reviewers independently screened titles and abstracts, excluding any that did not satisfy the eligibility criteria. Disagreements were resolved by discussion, and via third (senior) reviewer arbitration. Articles of interest were selected for

full-text assessment; if there was any doubt regarding eligibility, the full-text article was retrieved. Two reviewers independently assessed full-text articles against the eligibility criteria. A PRISMA flowchart is included in Figure 1. Two reviewers independently extracted data using pre-piloted forms. Where reported, secondary outcome data including: (i) the definition and prevalence of non-standard retinopathy features and (ii) the definition and prevalence of maculopathy features, were recorded. Prevalence estimates for co-morbid ocular pathology (e.g., cataract) and cardiovascular risk factors (e.g., hypertension, metabolic syndrome) were also recorded.

5.5 Risk of bias assessment: All eligible studies were assessed using a modified critical appraisal tool (Appendix S2). The tool features nine questions, each scoring 0 or 1, to assess selection, non-response, measurement and data analysis biases [21]. Quality assessment was conducted by two reviewers independently, with disagreements resolved by discussion. Judgments on the overall risk of bias were based on the total score for each article: 0-3 considered 'low', 4-6 considered 'moderate' and ≥7 considered 'high risk', based on the reviewers' subjective judgment of the preceding nine items [21].

5.6 Data analysis: Data were analysed using Review Manager 5 (The Cochrane Collaboration, Copenhagen, Denmark) and Microsoft Excel 2016 (Microsoft, Redmond, USA). Heterogeneity between included studies was assessed on study design, populations and methods used to measure outcomes. Statistical heterogeneity was assessed using the I^2 statistic and by visual inspection of forest plots [20]. Subgroup analyses of the primary outcome were conducted on the following covariates: (i) WHO region; (ii) age, gender, ethnicity; (iii) time since diagnosis of prediabetes; (iv) subtype of prediabetes (e.g., IGT); (v) grade of retinopathy; (vi) comorbid ocular pathology (e.g., cataract); (vii) comorbid cardiovascular risk factors (e.g., hypertension);

(viii) method or criteria used to diagnose prediabetes and (ix) method used to diagnose retinopathy.

5.7 Grading of evidence: The certainty of the evidence was assessed using the GRADE approach, detailed in Table S1 [18,24].

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The peer-reviewed protocol for this systematic review.

HIGHLIGHTS

- This systematic review found the prevalence of retinopathy in prediabetes was 7.1%.
- This represents an excess prevalence versus those with normoglycaemia.
- Hyperglycaemia can cause retinal damage prior to the diagnosis of diabetes.

CONTRIBUTION STATEMENT

All authors meet the ICMJE uniform requirements for authorship. VK, JE, UA, RAM and TLJ conceived the topic of this systematic review. VK and PN designed the search strategies, reviewed by an expert information specialist (IG), JE and SN. VK and PN performed the searches, data collection and data extraction with senior oversight from UA, JE and SN. SN provided statistical oversight of the data analysis. All authors were involved in the drafting, revision and final approval of the article to be published.

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DECLARATION OF INTEREST

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

DATA AVAILABILITY

All data generated or analysed during this study are included in this published article and its accompanying electronic supplementary material file.

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TABLE AND FIGURE LEGENDS

Table 1. Characteristics of included studies.

Footnotes: C, cohort study; **CS**, cross-sectional study; **HA**, Hispanic; **HB**, hospital-based; **IFG**, impaired fasting glucose; **IGT**, impaired glucose tolerance; **NGT**, normal glucose tolerance; **NHB**, non-Hispanic Black; **NHW**, non-Hispanic White; **nT2DM**, new or screen-detected type 2 diabetes mellitus; **PB**, population-based; **PD**, prediabetes; **T2DM**, known type 2 diabetes mellitus. * data not reported; † aggregate value including other study groups (e.g., NGT, T2DM); ‡ mean value ± 95% confidence intervals; § median value with ranges in brackets; ** prediabetes group defined by HbA1c criteria only.

Table 2. Prevalence of retinopathy in prediabetes from included studies.

Footnotes: ADA, American Diabetes Association; **CSMO**, clinically-significant macular oedema; **DRDSS**, Diabetic Retinopathy Disease Severity Scale; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **ICDRSS**, International Clinical Diabetic Retinopathy Severity Scale; **HE**, hard exudate; **IFG**, impaired fasting glucose; **IGT**, impaired glucose tolerance; **NGT**, normal glucose tolerance; **NSC**, National Screening Committee (UK); **PD**, prediabetes; **PDR**, proliferative diabetic retinopathy; **WES-DR**, Wisconsin Epidemiologic Study of Diabetic Retinopathy; **WHO**, World Health Organization. * data not reported; † additional data available for ethnicity-specific prevalence figures; ‡ IFG defined as ≥5.6 and <6.1 mmol/l; ** prediabetes group defined by HbA1c criteria only.

Figure 1. PRISMA flowchart of study selection process.

Figure 2. Forest plot of the prevalence of retinopathy in prediabetes from included studies.

Footnotes: * Prediabetes group size estimated from reported retinopathy prevalence and number of affected individuals. ** Aggregate prevalence estimates presented for impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and combined impaired fasting glucose with impaired glucose tolerance (IFG-IGT), (CI) confidence interval. All studies are population-based, except three hospital-based studies (blue highlights) and two randomised-controlled trials (green highlights). Box size proportional to precision.

Figure 3. Forest plot of the prevalence of retinopathy in prediabetes and normal glucose tolerance from included studies reporting data for both groups.

Footnotes: Normal glucose tolerance (NGT) prevalence estimates in blue, prediabetes prevalence estimates in red. [a] Prediabetes group size estimated from reported retinopathy prevalence and number of affected individuals. [b] Impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and combined impaired fasting glucose with impaired glucose tolerance (IFG/IGT) retinopathy prevalence estimates aggregated with total prediabetes group size used for 95% confidence interval (CI) estimation. [c] NGT group size estimated from the total study sample minus the reported prediabetes population. [d] Prediabetes group size estimated from reported retinopathy prevalence and number of affected individuals. All studies are population-based, except two hospital-based studies (blue highlights). Box size proportional to precision.