National Institute for Health and Care Excellence

Final

Diabetic retinopathy: management and monitoring:

[A] Evidence reviews for prognostic factors for progression of non-proliferative diabetic retinopathy to proliferative diabetic retinopathy and diabetic macular oedema

NICE guideline NG242

Evidence reviews underpinning recommendations 1.1.3 to 1.1.5 and research recommendation 2 in the NICE guideline

August 2024

Final

These evidence reviews were developed by NICE

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Contents

1 Prognostic factors for the progression of non-proliferative diabetic retinopathy

1.1 Review question

What are the prognostic factors for the progression of non-proliferative diabetic retinopathy in people with diabetic retinopathy to?

- proliferative diabetic retinopathy
- diabetic macular oedema
- diabetic macular ischaemia

1.1.1 Introduction

For people with diabetes, previous research has suggested that poor glycaemic control and hypertension are established risk factors for developing diabetic retinal disease in type I diabetes. This review assessed whether other risk factors can predict the progression from non-proliferative diabetic retinopathy to proliferative diabetic retinopathy, diabetic macular oedema, or diabetic macular ischemia. Many studies have examined the risk factors for developing any sight-threatening retinopathy, but few studies have focused on the risks of developing maculopathy. This review aimed to identify the risk factors associated with the development of diabetic maculopathy or diabetic proliferative disease. Predicting who is most at risk of progression is important to help determine who should receive more frequent monitoring and earlier treatment.

1.1.2 Summary of the protocol

Table 1. Summary of the PICO

Population	People with non-proliferative diabetic retinopathy
Prognostic factor	• Age • Gender • Ethnicity • Socio-economic status • Smoking habits • presence/absence of cardiovascular disease • cerebrovascular disease • nephropathy and specifically chronic kidney failure (defined as estimated glomerular filtration rate (GFR) of < 60 mL/min/1.73 m2), • peripheral neuropathy and specifically foot ulcers, amputation • body mass index (BMI) • neck/waist circumference • glycated haemoglobin • blood pressure • cholesterol and triglyceride • Anatomical changes in the retina (for example venous beading, cotton wool spots, venous looping, intraretinal microvascular abnormality, microaneurysms, exudates, dot-blot haemorrhages, neovascularisation) • Sleep apnoea • Duration of diabetes

	• Learning disability or mental health issue • Pregnancy
Reference standard	Progression to: • Proliferative diabetic retinopathy (treatment for diabetic retinopathy will be taken as a surrogate measure of progression). • Diabetic macular oedema (treatment for diabetic macular oedema will be taken as a surrogate measure of development of macular oedema) • Diabetic macular ischaemia
Outcomes	Outcomes to be predicted: • Proliferative diabetic retinopathy • Diabetic macular oedema • Diabetic macular ischaemia Adjusted odds ratios, risk ratios, hazard ratios will be used as a measure of association between the predictors and reference standard (outcomes to be predicted) Outcomes will be reported at the latest time point reported by the study.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

A Cochrane review (Perais et al. 2020) was identified which assessed prognostic risk factors for predicting the development of proliferative diabetic retinopathy. Results from this Cochrane review were used for the part of this review which covers risk factors for progression from non-proliferative diabetic retinopathy to proliferative diabetic retinopathy. The review was judged to be high quality and directly applicable to the review (see Appendix D) and so information for this part of the review was taken directly from the Cochrane review, rather than undertaking a new literature search or data analysis (see Table 2 in the methods document). The Cochrane review searched for a wider list of prognostic factors than were included in this review. It also included study types that were not included within the current review protocol, such as case-control studies. Studies that reported on the same outcomes but adjusted for different factors were reported separately, rather than combined into a meta-analysis. Only the 27 studies from the Cochrane review that matched the protocol for this review have been included and reported here.

The section of the review for progression to diabetic macular oedema or macular ischemia originally planned to include only studies consisting of cohorts of patients with non-proliferative diabetic retinopathy at baseline. However, on evaluation of potentially eligible studies and prior to commencing data extraction, it was decided to make a protocol deviation to incorporate those in which a proportion had no retinopathy, or proliferative diabetic retinopathy at baseline. This is because it became apparent that most studies included assorted populations of patients with and without diabetic retinopathy at baseline. The committee agreed that this would be appropriate and so studies with these mixed populations were included in the review and downgraded for applicability.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Prognostic evidence

1.1.4.1 Included studies.

A search was carried out to identify studies which evaluated risk factors for progression to diabetic macular oedema and diabetic macular ischemia. 2279 results were identified, of which 54 were identified as potential included studies at abstract level. Full text articles were ordered and reviewed against the inclusion criteria, of which 3 met the inclusion criteria for this review. Three multivariate prospective cohort studies were identified, each of which considered the progression from non-proliferative diabetic retinopathy to diabetic macular oedema. None of the evidence reported prognostic factors for progression to diabetic macular ischemia.

All the studies in the Cochrane review were assessed and 27 matched the prognostic factors and study design in the review.

Prognostic factors for progression to proliferative diabetic retinopathy (some studies reported on more than one prognostic factor):

- Evidence from 1 study – socioeconomic status,
- Evidence from 2 studies – cholesterol, triglycerides, estimated glomerular filtration rate, diabetic retinopathy features at baseline.
- Evidence from 3 studies – ethnicity, diabetic retinopathy severity at baseline
- Evidence from 4 studies – gender, duration of diabetes, diastolic blood pressure, systolic blood pressure
- Evidence from 5 studies – BMI
- Evidence from 6 studies - smoking
- Evidence from 13 studies – HbA1C

Prognostic factors for progression to diabetic macular oedema:

- Evidence from 1 study – gender, diastolic blood pressure, systolic blood pressure, cholesterol, triglycerides, estimated glomerular filtration rate, hypertension.
- Evidence from 2 studies - HbA1C

See Appendix C for the study selection flow chart.

1.4.2 Excluded studies.

51 studies were excluded following examination of the full text articles.

See Appendix I for excluded studies and reasons for exclusion.

1.1.5 Summary of studies included in the prognostic evidence.

Table 2: Prognostic factors for progression to proliferative diabetic retinopathy included from Cochrane review.

Study	Study type and follow-up time	Population	Prognostic factors
Cho 2019 (n= 1527)	• Retrospective cohort • Duration of follow-up: 4 years	Inclusion criteria: • T2D • underwent fundus photographic examinations for DR. • renal profiles were studied between August 2006 and February 2014. Exclusion criteria: • Estimated glomerular filtration rate < 15 ml/min/1:73 m2 • without follow-up renal profiles • fundus exam obtained more than 3 months after the first evaluation.	• eGFR • Age at baseline • Diabetes duration • Fasting plasma glucose • HbA1c
Gange 2021 (n=277,401)	• Retrospective cohort • Duration of follow-up: NR	Inclusion criteria: • insured patients aged ≥18 years. • newly diagnosed T2D; continuous enrolment for 12-months without a diabetes diagnosis • any diabetes medication use. Exclusion criteria: • Concurrent pregnancy • gestational diabetes • T1D • use of an insulin pump • diagnosis of diabetic eye disease prior to the diagnosis of diabetes.	• Age at DM diagnosis • Gender • Race • Socio-economic status • Hypertension • Smoking history • Insulin • HbA1c
Grauslund 2009a (n= 573)	• Retrospective cohort • Duration of follow-up: NR	Inclusion criteria: • All T1D patients from Fyn County, Denmark, • DM onset before 30 years of age, • identified based on insulin prescription as of 1 July 1973. Exclusion criteria: Not reported.	• Systolic BP • Diastolic BP • BMI • DR Status at BL • Maculopathy • Diabetes duration

Study	Study type and follow-up time	Population	Prognostic factors
			• HbA1c • Proteinuria • Smoking history
Harris 2013 (n=4617)	• Retrospective cohort • Duration of follow-up: NR	Inclusion criteria: • New diagnosis of NPDR after first year in registry (point of baseline) • aged ≥ 30 years. • ≥ 2 registrations as having diagnosis of DM; continuous enrolment in registry. • ≥1 visit to an ophthalmologist or optometrist during first year of registration. • no signs of NPDR or PDR; ≥ one record of HbA1c following baseline date. Exclusion criteria: • In registry <1 year; not in registry continuously • any record of PDR prior to index date.	• Insulin • Age at baseline • Gender • Race
Hsieh 2018 (n=2135)	• Retrospective cohort • Duration of follow-up: 5 year	Inclusion criteria: • Patients who received a diagnosis of T2D and underwent treatment between April 2002 and September 2004. Exclusion criteria: • Lost to follow-up within 6-months. • Ungradable image results from both eyes at baseline.	• eGFR
Janghorbani 2000 (n=3482)	• Retrospective cohort • Duration of follow-up:	Inclusion criteria: • NIDDM or IDDM • free of PDR (including those with no retinopathy and those with NPDR at registration) • complete data available. Exclusion criteria: • Secondary diabetes type of diabetes unknown	• Diabetes duration • HbA1c • Systolic BP
Jeng 2016 (n=53453)	• Retrospective cohort	Inclusion criteria:	• Gender

Study	Study type and follow-up time	Population	Prognostic factors
	• Duration of follow-up:	• Diabetic nephropathy (DN) cohort≥ 18-year-old patients with DM plus DN diagnosed between 01/01/00 and 31/12/10. • Non-DN cohort: diagnosis of DN not made during 01/01/00 and 31/12/10. Exclusion criteria: Not reported.	• Age at baseline • Hypertension • History of CVD • DR Status at BL
Kalter-Leibovici 1991 (n=330)	• Retrospective cohort • Duration of follow-up:	Inclusion criteria: • Diabetes type: T1D. • All Jewish patients attending centre with early-onset IDDM before 30 years of age. • DM duration of ≥ 10 yrs. Exclusion criteria: Not reported.	• Socio-economic status • HbA1c • Diabetes duration • Race
Keen 2001 (n=4483)	• Retrospective cohort • Duration of follow-up:	Inclusion criteria: • Diabetes type: T1D and T2D. • The study protocol required equal numbers of men and women with diabetes, sampled from three age bands within the range 35 to 54 years. Exclusion criteria: Not reported.	• Gender • Age at baseline • Diabetes duration • Systolic BP • Diastolic BP • Cholesterol • BMI • Smoking history • Insulin • Fasting plasma glucose • Age at DM diagnosis • Diabetes type
Kim 1998 (n=56)	• Retrospective cohort • Duration of follow-up: NR	Inclusion criteria: • Diabetes type: T2D. • Pts attending a university hospital (the Asan Medical Centre) in Seoul, Korea • NIDDM diagnosis • no episodes of ketoacidosis, • a diagnosis of diabetes after 30 years of age and treatment by diet and/or oral hypoglycaemic agents	• Cholesterol • Triglyceride • HbA1c • Diabetes duration • Age at baseline • BMI

Study	Study type and follow-up time	Population	Prognostic factors
		• fasting serum C-peptide values >0.30 nmol/L in patients using insulin Exclusion criteria: Not reported.	
Kim 2014 (n=452)	• Retrospective cohort • Duration of follow-up: NR	Inclusion criteria: • Diabetes type: T2D • Patients who were diagnosed and followed for more than 5 years annually or more often at a hospital-based dia-betic clinic (Asan Medical Centre, Seoul, Korea) Exclusion criteria: • PDR at the initial examination, • concomitant ocular disease other than DR • history of ocular trauma intraocular surgery	• Age at baseline • Diabetes duration • BMI • Fasting blood sugar • HbA1c • SD of HbA1c • Systolic BP • Diastolic BP • Cholesterol • Triglyceride
Klein 1984 (n=191)	• Retrospective cohort • Duration of follow-up: NR	Inclusion criteria: • Diabetes type: T1D • On insulin since DM diagnosis • if asymptomatic and diagnosed through routine examination must have become symptomatic and taken insulin within one year of diagnosis • ≥ 5 years duration; under care of cooperating GPs for at least 2/3 of the duration of DM. Exclusion criteria: Overweight; ≥ 50 years.	• DR Status at BL • DR Features
Lee 1992 (n=354)	• Retrospective cohort • Duration of follow-up: NR	Inclusion criteria: • Diabetes type: T2D. • NIDDM (no further description); Oklahoma Indians examined at the Indian Health Service facilities in Oklahoma • FPG >7.8 mmol (140 mg/dl) or a 2-hour post-load blood glucose level >11.1 mmol (200 mg/dl); • diagnoses of DM between 1937 and 1980. Exclusion criteria: PDR at baseline.	• Diabetes duration • Cholesterol • Systolic BP • Age at baseline • Type of diabetes treatment • Systolic BP • Age at DM diagnosis

Study	Study type and follow-up time	Population	Prognostic factors
Lee 2017a (n=32553)	• Retrospective cohort • Duration of follow-up: NR	Inclusion criteria: • First-time presenters to eye providers after being referred from the UK national DR screening program. • at least 2 DR assessments. Exclusion criteria: • Anti–vascular endothelial growth factor injections during study period • eyes with neovascularization at baseline were excluded from survival analyses.	• DR Status at BL • DR Features
Lee 2021 (n=2626)	• Retrospective cohort • Duration of follow-up: NR	Inclusion criteria: • T2D with more than two fundus colour photography tests. Exclusion criteria: • Without T2D • no HbA1c or FPG tests within 14 days of the study start. • PDR.	• DR Status at BL • DR Features
Lloyd 1995 (n=496)	• Retrospective cohort • Duration of follow-up:NR	Inclusion criteria: • Childhood-onset < 17 years Hospital of Pittsburgh between January 1950 and May 1980 Exclusion criteria: Not reported.	• Glycosylated haemoglobin • Triglyceride • Diastolic BP • Diabetes duration • DR Status at BL
Nelson 1989	• prospective cohort • Duration of follow-up: NR	Inclusion criteria: all diabetic people who lived in the Gila River Indian Community at any time between 13 October 1983 and 30 November 1987; whose heritage was at least 50% Pima, Papago, or a mixture of these closely related tribes; and who had undergone biennial research examinations. Exclusion criteria: not reported	• HbA1c • DR severity at baseline • Gender
Okudaira 2000 (n=527)	• Retrospective cohort • Duration of follow-up: NR	Inclusion criteria: • Patients who first visited the outpatient clinic between 1980 and 1989 • patients exhibited neither proteinuria nor PDR at the first visit; • patients who were seen at the clinic for at least 1 year	• Age at DM diagnosis • Age at baseline • Diabetes duration • BMI • Smoking history • HbA1c

Study	Study type and follow-up time	Population	Prognostic factors
		• patients who underwent fundus examination through dilated pupils by ophthalmologists at least once a year during the follow-up. Exclusion criteria: Not reported.	• Diastolic BP • Systolic BP • Cholesterol • Triglyceride
Porta 2001 (n=3250)	• Retrospective cohort • Duration of follow-up: NR	inclusion criteria: • Diagnosed T1D < 36 years. • insulin within 1 year onset • age 15-60 years. Exclusion criteria: • Centre drop-out • no retinal photo at baseline at follow-up • PDR at baseline.	• Diastolic BP • Age at DM diagnosis • Diabetes duration • HbA1c • DR Status at BL
Roy 2006 (n=725)	• Retrospective cohort • Duration of follow-up: NR	Inclusion criteria: • African Americans with T1D; Treated with insulin before 30 years of age. • receiving insulin at time of study • participated in the New Jersey 725 study 1993-1998. Exclusion criteria: • T2D; diagnosed after 30 years; maturity-onset diabetes of youth.	• HbA1c • age at baseline • Hypertension • Diastolic BP
Skrivarhaug 2006 (n=368)	• Retrospective cohort • Duration of follow-up: NR	Inclusion criteria: • All new-onset cases of T1D in Norway in children below 15 years of age • between 1973 and 1982 • examined for DR at baseline. Exclusion criteria: Not reported.	• Gender • Diabetes duration • Mean age at PDR diagnosis • Mean diabetes duration at PDR diagnosis • HbA1c • Triglyceride • DR Status at BL
WESDR (n=2366)	• Retrospective cohort • Duration of follow-up: NR	Inclusion criteria: • Younger-onset group: • IDD before 30 years.	• Diabetes duration • Age • Gender • Diabetes duration

Study	Study type and follow-up time	Population	Prognostic factors
		• Older onset: Diagnosed with DM at 30 years or older and diagnosis. • postprandial serum glucose level of at least 11.1 mmol/L • a fasting serum glucose level of 7.8 mmol/L or greater on at least two occasions. Exclusion criteria: Not reported.	• HbA1c • Systolic BP • Diastolic BP • BMI • Triglyceride • Smoking history

Table 3: Included studies of prognostic factors for progression to diabetic macular oedema (NICE review)

Study	Study type and follow-up time	Population	Prognostic factors
Hammes, 2015 (n= 64784)	• Prospective cohort • Duration of follow-up: NR	Inclusion criteria: • Type 2 diabetes • age at disease onset was above 40 years. • at least one retinal examination had been documented. Exclusion criteria: • younger than 40 years of age	• Age • Diabetes Duration • Gender • Hba1c Hypertension • Smoking
Hsieh 2018 (n= 2135)	• prospective cohort • Duration of follow-up: 8-year	Inclusion criteria: • Type 2 Diabetes. • Patients With Gradable Image Exclusion criteria: • Patients with ungradable image results from both eyes at baseline	• Estimated Glomerular Filtration Rate (eGFR) • Body Mass Index • Systolic Blood Pressure (SBP), • Diastolic Blood Pressure • Haemoglobin A1c (Hba1c) • Fasting Glucose Level • Total Cholesterol Level • Triglyceride Level
Lobo, 2018 (n=205)	• Prospective cohort	Inclusion criteria: • Diabetes type 2 • aged over 35 years,	• Age • Gender • HbA1c

Study	Study type and follow-up time	Population	Prognostic factors
	• Duration of follow-up: 2 years	• mild NPDR (levels 20–35, according (ETDRS) diabetic retinopathy severity scale) • best-corrected visual acuity (BCVA) >20/25 on the ETDRS chart • HbA1C ≤11%, with no previous treatment with laser or anti-VEGF or steroid intravitreal injection • no other retinal vascular disease or glaucoma • inadequate ocular media and/or pupil dilatation • that did not permit good-quality fundus photography. Exclusion criteria: • Not reported	• Systolic Blood Pressure • Diastolic Blood Pressure • Cholesterol • Triglycerides

See Appendix D for full evidence tables.

1.1.6 Summary of the evidence

People progressing to proliferative diabetic retinopathy

Data from the Cochrane review (Perais et al. 2020)

Table 4: Gender - Studies undertaking multivariable regression analyses to determine the effect of gender on progression to proliferative diabetic retinopathy

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 2 diabetes (Male vs female)			
RR >1 indicates risk factor of progression to proliferative diabetic retinopathy at 4 years			
1 Nelson 1989	953	Adjusted RR: 1.5 (0.7 3.4)	Moderate
Type 1 and 2 diabetes (Male vs female)			
1 Lee 2017	32,553	Adjusted HR: 0.92 (0.71-1.19)[1]	Moderate
HR >1 indicates risk factor of progression to proliferative diabetic retinopathy at 5 years			
1 Harris 2013	4,617	Adjusted HR: 1.08 (0.94-1.22)	Moderate
HR >1 indicates risk factor of progression to proliferative diabetic retinopathy at 5 years (Female vs male)			
1 Jeng 2016	53,453	Adjusted HR: 0.99 (0.85-1.15)	Moderate

Table 5: Race -Studies undertaking multivariable regression analyses to determine the effect of race on progression to PDR.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 1 diabetes African American race vs. Caucasian HR/OR >1 indicates risk factor of progression to proliferative diabetic retinopathy at 5 years			
1 Arfken 1998	312	Adjusted OR: 0.73 (0.30-1.78)	Very low
Type 2 Diabetes Non-Caucasian vs. Caucasian			
1 Lee 2017a	32,553	Adjusted HR: 0.94 (0.89-1.00)	Very low
Type 1 and type 2 diabetes Black			
Harris 2013	4617	Adjusted HR: 1.29 (0.92-1.82)	Very low

No. of studies	Sample size	Effect size (95%CI)	Quality
Latino			
Harris 2013	4617	Adjusted HR: 1.12 (0.76-1.65)	Very low
Asian			
Harris 2013	4617	Adjusted HR: 1.35 (0.73-2.49)	Very low

Table 6: Duration of diabetes -Studies undertaking multivariable regression analyses to determine the effect of duration of diabetes on progression to PDR:

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 1 diabetes RR >1 indicates risk factor of progression to proliferative diabetic retinopathy			
Lloyd 1995	496	Adjusted RR: 1.03 (0.94-1.12)	Very low
4-7 years vs. <4 years			
Janghorbani 2000	1349	Adjusted RR: 0.78 (0.43-1.41)	Very low
8-11 years vs. <4 years			
Janghorbani 2000	1349	Adjusted RR: 1.95 (1.23-3.09)	Very low
≥12 years vs. <4 years			
Janghorbani 2000	1349	Adjusted RR: 3.05 (2.09-4.45)	Very low
Increasing duration of diabetes			
Kalter-Leibovici 1991	330	Adjusted OR: 1.20 (1.1-1.3)	Very low
Per 10 years			
Grauslund 2009a	573	Adjusted OR: 0.69 (0.35-1.36)	Very low
Type 2 diabetes OR >1 indicates risk factor of progression to proliferative diabetic retinopathy at 5 years			
Mean duration of diabetes at 2 years follows up			
Gui 2013	205	Adjusted OR:1.18 (1.13-1.25)	Very low
12 years vs. <4 years, taking insulin			
Janghorbani 2000	2133	Adjusted OR: 1.77 (1.15-2.72)	Very low
12 years vs. <4 years, not taking insulin			
Janghorbani 2000	2133	Adjusted OR: 1.37 (0.83-2.26)	Very low
Type 1 and type 2 diabetes			
Duration of diabetes 8-11 years			

No. of studies	Sample size	Effect size (95%CI)	Quality
Janghorbani 2000	3482	Adjusted RR: 1.42 (1.10-1.83)	Very low
Duration of diabetes ≥12 years			
Janghorbani 2000	4483	Adjusted RR 1.95 (1.58-2.39)	Very low

Table 7: Socio-economic status -Studies undertaking multivariable regression analyses to determine the effect of socio-economic status on progression to PDR.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 1 diabetes OR >1 indicates risk factor of progression to proliferative diabetic retinopathy at 4 years. (Per 10-point increase) Females Per 10-point increase			
WESDR	996	Adjusted OR: 0.78 (0.52-1.18)	Very low
Klein 1994	996	Adjusted OR: 0.79 (0.46-1.37)	Very low
OR >1 indicates risk factor of progression to proliferative diabetic retinopathy at 4 years. (Per 10-point increase) Males Per 10-point increase			
WESDR	1370	Adjusted OR: 0.84 (0.58-1.23)	Very low
Klein 1994	1370	Adjusted OR: 0.88 (0.55-1.41)[1]	Very low

Table 8: HbA1c -Studies undertaking multivariable regression analyses to determine the effect of HbA1c on progression to PDR.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 1 diabetes OR/RR>1 indicates risk factor of progression to proliferative diabetic retinopathy. Top quartile compared to other three quartiles			
Lloyd 1995	496	Adjusted RR: 5.75 (1.54-21.4)	Moderate
HbA1c Per 1% increase			
Klein 1984	996	Adjusted RR: 1.5 (1.4-1.8)	Moderate
HbA1c ≥11 relative to <11%			
Janghorbani 2000	1349	Adjusted RR: 1.32 (1.22-1.43)	Moderate
HbA1c Per 1% increase			
Roy 2006	725	Adjusted OR: 1.32 (1.22-1.43)	Moderate
HbA1c Per 2% increase			
Arfken 1998	312	Adjusted OR: 1.92 (1.36-2.7)	Moderate

No. of studies	Sample size	Effect size (95%CI)	Quality
HbA1c Per 1% increase At 10 years			
WESDR Klein 1994	334	Adjusted OR: 1.9 (1.7-2.2)	Moderate
At 14 years			
WESDR Klein 1994	996	Adjusted OR: 1.81 (1.6-2.05)	Moderate
At 24 years			
WESDR Klein 1994	955	Adjusted HR: 1.38 (1.31-1.46)	Moderate
Type 2 diabetes			
Older onset taking insulin Per 1% increase			
WESDR Klein 1994	1370	Adjusted OR: 1.30 (1.00-1.60)	Moderate
HbA1c Per 1% increase			
Cho 2019	1527	Adjusted OR: 1.11 (0.93-1.32)	Moderate
Mean HbA1c during follow-up			
Kim 1998	228	Adjusted RR: 1.30 (1.04-1.61)	Moderate
Maximum >9% vs <6.5%			
Gange 2021	71815	Adjusted OR: 2.10 (1.64-2.69)	Moderate
HR >1 indicates higher HbA1c is a risk factor of progression to proliferative diabetic retinopathy			
Mean HbA1c			
Okudaira 2000	527	Adjusted HR: 1.43 (1.23-1.67)	Moderate
HbA1c Per one SD			
Lee 2021	2623	Adjusted: HR: 1.09 0.97-1.22	Moderate
HbA1c Per unit increase			
Kim 2014	452	Adjusted HR: 1.19 (1.10-1.46)	Moderate
Older-onset, (40 >) taking insulin and Older-onset, (40>) not taking insulin Per 1% increase			
WESDR Klein 1994	996	Insulin: Adjusted OR: 0.79 (0.46-1.37)[6] Non-insulin Adjusted OR: 0.78 (0.52-1.18)[6]	Moderate
10-year HbA1c			
Kalter-Leibovici 1991	330	Adjusted OR: 1.9 (1.4-2.5)	Moderate
Type 1 and type 2 diabetes			
With increasing HbA1c at 5 years			
Harris 2013	4617	Adjusted HR: 1.14 (1.07-1.21)	Moderate
HbA1c ≥11			
Janghorbani 2000	3482	Adjusted RR 1.33 (1.13-1.53)	Moderate

Table 9: Diastolic blood pressure -Studies undertaking multivariable regression analyses to determine the effect of diastolic blood pressure on progression to PDR.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 1 diabetes			
OR>1 indicates risk factor of progression to proliferative diabetic retinopathy			
79 to ≥86 mmHg			
Roy 2006	725	Adjusted OR: 2.5 (1.04-6.00)	Very low
Per 10 mmHg Per increase in one year			
Grauslund 2009a	573	Adjusted OR: 1.31 (0.86-1.99)	Very low
Type 2 diabetes			
Per unit increase			
Okudaira 2000	527	Adjusted HR: 1.15 (1.01-1.31)	Very low
Per one SD			
Lee 2021	2623	Adjusted HR: 1.03 (1.00-1.05)	Very low

Table 10: Fasting plasma glucose -Studies undertaking multivariable regression analyses to determine the effect of fasting plasma glucose on progression to PDR.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 2 diabetes OR>1 indicates Fasting plasma glucose is a risk factor of progression to proliferative diabetic retinopathy. Fasting plasma glucose			
Lee 2021	2623	Adjusted HR: 0.93 (0.82-1.06)	Very low

Table 11: Systolic blood pressure -Studies undertaking multivariable regression analyses to determine the effect of systolic blood pressure on progression to PDR.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 1 diabetes			
OR>1 indicates risk factor of progression to proliferative diabetic retinopathy			
Systolic blood pressure Increasing systolic blood pressure			
WESDR Klein 1994	996	Adjusted OR: 1.01 (0.99-1.03)	Very low
Systolic blood pressure >160mmHg			
Janghorbani 2000	1349	Adjusted RR: 1.61 (1.18-2.20)	Very low
Systolic blood pressure Per 10 mmHg			
WESDR Klein 1994	25	Adjusted HR: 1.14 (1.04-1.25)	Very low
Systolic blood pressure Per 10 mmHg			
Grauslund 2009a	527	Adjusted OR: 0.91 (0.69-1.20)	Very low

Table 12: Total cholesterol -Studies undertaking multivariable regression analyses to determine the effect of total cholesterol on progression to PDR.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 2 diabetes			
OR>1 indicates risk factor of progression to proliferative diabetic retinopathy			
Total cholesterol ≥4.8 vs <4.8 mM			
Lee 2021	2623	Adjusted HR: 0.93 (0.81-1.07)	Very low
Total cholesterol increases Per one SD			
Nelson 1989	953	Adjusted RR: 1.80 (1.2-2.7)	Very low

Table 13: Triglycerides -Studies undertaking multivariable regression analyses to determine the effect of triglycerides on progression to PDR.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 1 diabetes			
OR>1 indicates risk factor of progression to proliferative diabetic retinopathy			
With increasing triglyceride level			
Skrivarhaug 2006	368	Adjusted RR: 1.55 1.06-1.95	Low
Type 2 diabetes			
Per one SD			
Lee 2021	2623	Adjusted HR: 1.01 (0.91-1.12)	Low

Table 14: Estimated glomerular filtration rate (eGFR) -Studies undertaking multivariable regression analyses to determine the effect of eGFR on progression to PDR.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 2 diabetes HR >1 indicates risk factor of progression to proliferative diabetic retinopathy			
a reduction in eGFR of >20%			
Cho 2019	405	Adjusted HR: 2.55 (1.22-5.35)	Moderate
(eGFR) 46-60mL/min/1.73m2			
Hsieh 2018	2096	Adjusted HR: 1.55(0.63-3.82)	Moderate
(eGFR) 30-45mL/min/1.73m2			
Hsieh 2018	2096	Adjusted HR: 2.05 (0.72-5.86)	Moderate
(eGFR) <30 mL/min/1.73m2			
Hsieh 2018	2096	Adjusted HR: 4.22 (1.27-14.07)	Moderate

Table 15: Diabetic retinopathy severity at baseline -Studies undertaking multivariable regression analyses to determine the effect of diabetic retinopathy severity at baseline on progression to PDR.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 1 diabetes OR >1 indicates risk factor of progression to proliferative diabetic retinopathy			
Lloyd 1995	322	Adjusted RR: 5.99 (3.03-11.9)	Moderate
Worsening baseline severity			
Porta 2001	2013	Adjusted OR: 10.1 (5.9-17.2)	Moderate
WESDR	996	Adjusted OR: 1.38 (1.29-1.48)	Moderate
Type 2 diabetes			
Mild NPDR			
Lee 2021	2623	Adjusted HR: 13.58 (6.07-30.39)	Moderate
Moderate NPDR			
Lee 2021	2623	Adjusted HR: 23.09 (10.68-49.91)	Moderate
Severe NPDR			
Lee 2021	2623	Adjusted HR: 55.24 (25.54-119.46)	Moderate
Type 1 and type 2 diabetes			
Very mild NPDR			
Lee 2021	2623	Adjusted HR: 4.02 (3.25-4.96)	Moderate
mild NPDR			
Lee 2021	2623	Adjusted HR: 6.71 (5.46-8.24)	Moderate
Moderate NPDR			
Lee 2021	2623	Adjusted HR: 14.80 (12.10-18.09)	Moderate
Severe NPDR			
Lee 2021	2623	Adjusted HR: 28.19 (22.92-34.67)	Moderate
Very severe NPDR			
Lee 2021	2623	Adjusted HR: 58.42 (46.95-72.70)	Moderate

Table 16: Diabetic retinopathy features at baseline -Studies undertaking multivariable regression analyses to determine the effect of diabetic retinopathy features at baseline on progression to PDR.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 1 and 2 diabetes OR >1 indicates risk factor of progression to proliferative diabetic retinopathy			
IRMA Intraretinal microvascular abnormalities vs. venous beading in four quadrants			
Lee 2017a	2823	Adjusted HR: 1.77 (1.25-2.49)	Very low
Dot/blot haemorrhages vs venous beading in four quadrants			
Lee 2017a	2823	Adjusted HR: 1.47 (0.94-2.31)	Very low
Difference in number of microaneurysms at baseline and follow-up			
WESDR Klein 1995	236	Adjusted HR: 1.04(1.02-1.07)	Very low
Ratio between number of microaneurysms at baseline and follow-up			
WESDR Klein 1995	236	Adjusted HR: 1.05 (1.01-1.09)	Very low
Difference of ≥16 microaneurysms at baseline and follow-up			
WESDR Klein 1995	236	Adjusted HR: 5.77 (2.24-14.89)	Very low

Table 17: Body mass index (BMI) -Studies undertaking multivariable regression analyses to determine the effect of BMI on progression to PDR.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 1 diabetes OR >1 indicates risk factor of progression to proliferative diabetic retinopathy			
BMI - per increase 1 kg/m2			
Grauslund 2009a	573	Adjusted OR: 1.01 (0.86-1.20.9)	Very low
BMI per increase 4 kg/m2			
WESDR Report XXII	996	Adjusted HR: 1.21 (1.07-1.36)	Very low
Type 2 diabetes			
BMI = obesity at baseline (men:>31.0 kg/m2; women: >32.2 kg/ m2			
WESDR Report XXII	1370	Adjusted RR: 1.41 (0.76-2.62)	Very low
BMI ≥34 vs. < 34 kg/m2			
Nelson 1989	953	Adjusted RR: 1.0 (0.6-1.6)	Very low
Change in BMI during follow-up			
Kim 1998	56	Adjusted RR: 1.33 (0.87-1.50)	Very low
BMI per one SD			

No. of studies	Sample size	Effect size (95%CI)	Quality
Lee 2021	2623	Adjusted HR: 0.91 (0.79-1.03)	Very low

Table 18: Smoking -Studies undertaking multivariable regression analyses to determine the effect of smoking on progression to PDR.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 1 diabetes OR >1 indicates risk factor of progression to proliferative diabetic retinopathy			
Smoking Ever vs. never			
WESDR Moss 1996	799	Adjusted OR: 1.15 (0.6-2.2)	Very low
Current smoker			
WESDR Moss 1996	799	Adjusted OR: 0.86 (0.54-1.36)	Very low
Ex-smoker			
WESDR Moss 1996	799	Adjusted OR: 0.94 (0.51-1.75)	Very low
Current smoker			
Grauslund 2009a (Thorlund)	573	Adjusted OR: 1.9 (0.88-4.11)	Very low
Ex-smoker			
Grauslund 2009a (Thorlund)	573	Adjusted OR: 0.87 (0.28-2.67)	Very low
Diabetic pack years smoked per 10 years			
WESDR	996	Adjusted OR: 0.79 (0.66-0.95)	Very low
Type 2 diabetes			
% Smokers vs. non-smokers			
Gui 2013	205	Adjusted OR: 1.07 (1.04-1.11)	Very low
Smoking: yes vs. no			
Nelson 1989	953	Adjusted RR: 0.70 (0.2-1.9)	Very low
Smoking: Ever vs. never			
WESDR Moss 1991	1370	Adjusted OR: 1.13 (0.45-7.83)	Very low
Smoking			
Gange 2021	71817	Adjusted OR: 0.84 (0.7-1.0)	Very low
Insulin Ex-smoker			
WESDR Moss 1996	1370	Adjusted OR: 1.04 (0.49-2.22)	Very low
Insulin Current smoker			
WESDR Moss 1996	1370	Adjusted OR: 1.15 (0.47-2.8)	Very low

No. of studies	Sample size	Effect size (95%CI)	Quality
Non-insulin Ex-smoker			
WESDR Moss 1996	1370	Adjusted OR: 0.8 (0.23-2.8)	Very low
Non-insulin Current smoker			
WESDR Moss 1996	1370	Adjusted OR: 0.25 (0.03-2.06)	Very low

Summary of the prognostic evidence for progression to diabetic macular oedema

Data from the NICE review

Table 19: Gender - Studies undertaking multivariable regression analyses to determine the effect of gender on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 2 diabetes (Male vs female)			
OR >1 indicates risk factor of progression to DMO at 2 years			
1 (Lobo, 2018)	205	Adjusted OR: 4.09 (1.06–15.79)	Moderate

Table 20: HbA1c -Studies undertaking multivariable regression analyses to determine the effect of HbA1c on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 2 diabetes OR >1 indicates risk factor of progression to DMO			
HbA1c>8%			
Hammes, 2015	64784	Adjusted OR: 1,57 (1.288 1.903)	Low
HbA1c at 2 years follow up			
Lobo 2018	205	Adjusted OR: 0.56 (0.35–0.90)	Moderate

Table 21: Diastolic blood pressure -Studies undertaking multivariable regression analyses to determine the effect of diastolic blood pressure on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 2 diabetes- Diastolic blood pressure OR >1 indicates risk factor of progression to DMO			
Lobo 2018	205	Adjusted OR: 1.03 (0.95–1.12)	Moderate

Table 22: Systolic blood pressure -Studies undertaking multivariable regression analyses to determine the effect of systolic blood pressure on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 2 diabetes			
Systolic blood pressure OR >1 indicates risk factor of progression to DMO			
Lobo 2018	207	Adjusted OR: 0.96 (0.92–1.01)	Moderate

Table 23: Total cholesterol -Studies undertaking multivariable regression analyses to determine the effect of total cholesterol on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 2 diabetes			
Total cholesterol, mmol/L OR >1 indicates risk factor of progression to DMO			
Lobo 2018	205	Adjusted OR: 0.98 (0.95–1.01)	Moderate

Table 24: Triglycerides -Studies undertaking multivariable regression analyses to determine the effect of triglycerides on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 2 diabetes Triglycerides OR >1 indicates risk factor of progression to DMO			
Lobo 2018	205	Adjusted OR: (1.00 1.00–1.01)	Low

Table 25: Estimated glomerular filtration rate (eGFR) -Studies undertaking multivariable regression analyses to determine the effect of eGFR on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 2 diabetes HR >1 indicates risk factor of progression to DMO			
61-90 eGFR, mL/min/1.73m2			
Hsieh 2018	1055	Adjusted HR: 1.226 (0.711-2.115)	Low
46-60 eGFR, mL/min/1.73m2			
Hsieh 2018	418	Adjusted HR: 1.218 (0.559-2.654)	Low
30-45 eGFR, mL/min/1.73m2			
Hsieh 2018	248	Adjusted HR: 3.106 (1.268-7.609)	Low
<30 eGFR, mL/min/1.73m2			
Hsieh 2018	98	Adjusted HR: 1.849 (0.568-6.025)	Low

Table 26: Hypertension-Studies undertaking multivariable regression analyses to determine the effect of hypertension o on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Quality
Type 2 diabetes			
Hypotension (>140/80 mmHg) OR >1 indicates risk factor of hypertension on progression to macular oedema.			
1 (Hammes, 2015)	64784	Adjusted OR: 1.39 (1.11–1.74)	Low

See Appendix E for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies.

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (Appendix B). This search retrieved 672 studies. Based on title and abstract screening, 671 of the studies could confidently be excluded for this review question. One study was excluded following the full-text review. No relevant health economic studies were included.

1.1.7.2 Excluded studies.

See Appendix I for excluded studies and reasons for exclusion.

See the health economic study selection flow chart presented in Appendix F.

1.1.8 Summary of included economic evidence.

No relevant health economic studies were identified to be included.

1.1.9 Economic model

Original health economic modelling was not prioritised for this review question.

1.1.10 Unit costs

No unit costs have been considered as part of this review question.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee discussed that progression of non-proliferative diabetic retinopathy to proliferative diabetic retinopathy or diabetic macular oedema are important outcomes as they indicate the worsening of retinopathy which leads to other serious consequences, such as vision loss.

The committee wanted to consider evidence for the progression of non-proliferative diabetic retinopathy to diabetic macular ischemia but found no relevant studies.

1.1.11.2 The quality of the evidence

The evidence for the risk factors predicting progression from proliferative diabetic retinopathy to diabetic retinopathy ranged from moderate to very low quality, with most of the downgrading due to studies being at high to moderate risk of bias. More information about the quality of individual studies can be found in the Cochrane review (Perais et al. 2020).

Three studies investigated clinical prediction factors for the progression of non-proliferative retinopathy to diabetic macular oedema for people with type 2 diabetes. The evidence ranged from moderate to low quality. Studies were most commonly downgraded for studies being at moderate risk of bias, or being partially applicable to the review, due to mixed populations being included rather than just people with non-proliferative retinopathy. One study reported that it adjusted for confounding factors, but did not report which factors were adjusted for, making it more difficult for the

committee to interpret the results. There was no evidence on the prognostic factors for progression to diabetic macular oedema for people with type 1 diabetes.

The committee were unable to determine whether some factors, such as duration of diabetes, blood pressure and total cholesterol were risk factors for progression to proliferative diabetic retinopathy. For many of these factors, confidence intervals crossed the line of no effect. The committee noted that many of the studies did not adjust for important confounding factors, such as diabetic retinopathy severity at baseline. There was also variation in the reporting of important baseline characteristics, such as retinopathy severity at baseline and HbA1c. The committee were therefore limited in the recommendations that could be made due to uncertainty about the populations and methods used in the studies. They were also concerned that some of the confounding factors in the natural course of retinopathy were not being accounted for in the analysis.

Due the nature of the data, it was difficult to conduct meta-analysis. Each study differed according to the prognostic factors evaluated, time points of prognostic factor measurements and outcomes, and which confounding factors were adjusted for. As a result, much of the analysis was based on the results of single studies. Although some of the studies had very large sample sizes, the committee were concerned by other issues, such as either the choice of confounding factors that were adjusted for, or a lack of adjustment, and inconsistent results across different studies, The committee noted that there are a range of different factors that can influence the course of diabetic retinopathy, which made it difficult for the committee to be certain of which prognostic factors are most important to consider when assessing whether someone is at risk of progression.

There was no evidence for progression from non-proliferative diabetic retinopathy to diabetic macular ischemia. The committee thought this information was important and so this was included as part of a research recommendation (see Appendix J). This will enable recommendations to be made on this in future updates of the guideline.

1.1.11.3 Imprecision and clinical importance of effects.

The committee noted that some of the results had wide confidence intervals. This imprecision made it hard to be certain of the effects of different prognostic factors. Due the nature of the data it was difficult to conduct meta-analysis and it was therefore difficult for the committee to determine which factors best predict a person's risk of progression from non-proliferative diabetic retinopathy.

The committee agreed that the evidence for some of the prognostic factors for progression to proliferative diabetic retinopathy was precise enough to consider them risk factors for progression. Both severity of retinopathy and HbA1c levels were therefore listed as prognostic factors in the recommendations. Most of the evidence for other outcomes was based on single study analysis, with confidence intervals crossing the line of no effect. The committee could not be confident in whether these results indicated that other factors do not predict progression, or whether this was due to the limited number of studies for some comparisons, most of which had small sample sizes. A few results were from much larger studies, but the committee thought that the wide confidence intervals could partly reflect the factors that were selected for adjustment, rather than being a true reflection of the effect of a particular factor on progression of retinopathy. They therefore decided not to make further recommendations on progression to proliferative diabetic retinopathy. Instead, progression to proliferative diabetic retinopathy was included in the research recommendation (see Appendix J).

The evidence on diabetic macular oedema was mostly from small trials with a high degree of imprecision. A few studies included a larger number of participants, but for these studies, either confidence intervals crossed the line of no effect, or the committee had concerns about which factors were adjusted for in the analysis. Meta-analysis was not possible for any of the outcomes due to study heterogeneity, which further limited the conclusions that could be drawn.

1.1.11.4 Benefits and harms

Proliferative diabetic retinopathy

Higher HbA1c levels and severity of retinopathy at baseline were both shown to be predictors for the development of proliferative diabetic retinopathy in people with both type 1 and type 2 diabetes. The committee agreed that both factors are important and will help identify people who are at higher risk of progression.

There was also some evidence suggesting several markers for renal disease and triglyceride profiles in people with Type 1 diabetes were prognostic factors for progression. However, this evidence was low to very low quality, due to risk of bias in the included studies and inconsistency. The committee discussed that while this evidence was not high quality, their clinical knowledge and experience supported this being included in the recommendations as a risk factor that ophthalmologists should consider when deciding on a patient's needs for follow-up.

The committee discussed how the evidence and their clinical experience suggests that people with non-proliferative diabetic retinopathy and type 1 or type 2 diabetes should be encouraged to manage modifiable risk factures. This includes maintaining adequate glucose control and blood pressure, to prevent progression to proliferative diabetic retinopathy. The committee also discussed the need for closer monitoring and communication across the multidisciplinary healthcare teams, such as diabetologist and ophthalmologists, who support people with diabetes. This will enable clinicians who are involved in a person's wider diabetes management to access information about the status of a person's diabetic eye disease and take this into account when they are considering future treatment and monitoring.

Diabetic macular oedema

Moderate and low-quality evidence showed that gender, increasing HBA1c (>8%), hypertension, and an estimated globular filtration rate of 30-45 were all predictors of progression to diabetic macular oedema. However, given the limited evidence base noted in the section above on the quality of the evidence, the committee did not think they could confidently recommend each of these factors as risk factors for progression. Instead, they decided to recommend that ophthalmologists should consider stage of retinopathy when deciding on follow-up and interventions, as this reflects a combination of the above factors, and other factors, which tend to develop over the course of disease.

Moderate quality evidence did not show blood pressure, cholesterol or triglycerides to be predictors of progression of diabetic macular oedema. However, the committee were concerned that the evidence for each prognostic factor came from single studies, the majority of which did not correct for stage of retinopathy at baseline. The committee noted that, in their clinical experience, higher blood pressure is often considered a risk factor for progression to macular oedema. This was considered important, as it is something that a patient can modify if they are aware of the risks of progression. Due to the very limited evidence base, progression to diabetic macular oedema was also included in the research recommendation (see Appendix J).

Given the limited evidence available, the committee decided to make general recommendations about risk factors for the progression of non-proliferative diabetic retinopathy to either proliferative diabetic retinopathy or diabetic macular oedema. This was based on a combination of the evidence for proliferative diabetic retinopathy and the committee's clinical experience. Until there is more evidence to specify which factors make someone more at risk of progressing to either proliferative retinopathy or to macular oedema, they thought it was important to highlight factors that may be associated with progression in general. This will ensure that people are not overlooked for additional monitoring or treatment.

1.1.11.5 Cost effectiveness and resource use

No relevant economic evaluations were identified which addressed the cost effectiveness of the progression of non-proliferative diabetic retinopathy to proliferative diabetic retinopathy or diabetic macular oedema. The committee discussed that ophthalmologists should have access to a patient's HbA1c and blood pressure results for discussion with the patient. Educating the patient with information on how they can lower HbA1c, and blood pressure can give the patient the opportunity to reduce their risk of progression to proliferative diabetic retinopathy or diabetic macular oedema. This could lead to a reduction in resource impact by delaying or preventing progression of disease which has considerable cost and quality of life implications.

1.1.12 Recommendations supported by this evidence review.

This evidence review supports Recommendations 1.1.3 to 1.1.5 and the research recommendation on prognostic factors for the progression of non-proliferative diabetic retinopathy to proliferative diabetic retinopathy, diabetic macular oedema, or macular ischemia.

1.1.13 References – included studies

1.1.13.1 Effectiveness

Studies included from the NICE review

Hammes, H.-P., Welp, R., Kempe, H.-P. et al. (2015) Risk factors for retinopathy and DME in type 2 diabetes-results from the German/Austrian DPV database. PLoS ONE 10(7): e0132492

Hsieh, Yi-Ting, Tsai, Meng-Ju, Tu, Shih-Te et al. (2018) Association of Abnormal Renal Profiles and Proliferative Diabetic Retinopathy and Diabetic Macular Edema in an Asian Population With Type 2 Diabetes. JAMA ophthalmology 136(1): 68-74

Lobo, Conceicao, Pires, Isabel, Alves, Dalila et al. (2018) Subclinical Macular Edema as a Predictor of Progression to Central-Involved Macular Edema in Type 2 Diabetes. Ophthalmic research 60(1): 18-22

Included systematic review (Cochrane review)

Perais J, Agarwal R, Evans JR, Loveman E, Colquitt JL, Owens D, Hogg R, Lawrenson JG, Takwoingi Y, Lois N. Prognostic factors for the development and progression of proliferative diabetic retinopathy in people with diabetic retinopathy.

Cochrane Database of Systematic Reviews 2020, Issue 11. Art. No.: CD013775. DOI: 10.1002/14651858.CD013775.

Studies included from the Cochrane review (Perais et al., 2020)

Cho 2019 {published data only}

Cho A, Noh JW, Kim J. Progression of diabetic retinopathy and declining renal function in patients with type 2 diabetes. Journal of the American Society of Nephrology 2019;30:507.

Gange 2021 {published data only}

Gange WS, Lopez J, Xu BY, Lung K, Seabury SA, Toy BC. Incidence of Proliferative Diabetic Retinopathy and Other Neovascular Sequelae at 5 Years Following Diagnosis of Type 2 Diabetes. Diabetes Care 2021;44(11):2518-26.

Grauslund 2009a {published data only}

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Grauslund J, Green A, Sjølie AK. Prevalence and 25 year incidence of proliferative retinopathy among Danish type 1 diabetic patients. Diabetologia 2009;52(9):1829-35.

Harris 2013 {published data only}

Harris NK, Talwar N, Gardner TW, Wrobel JS, Herman WH, Stein JD. Predicting development of proliferative diabetic retinopathy. Diabetes Care 2013;36(6):1562-8.

Hsieh 2018 {published data only}

Hsieh Y-T, Hsieh M-C. Time-sequential correlations between diabetic kidney disease and diabetic retinopathy in type 2 diabetes - an 8-year prospective cohort study. Acta Ophthalmologica 2021;99(1):e1-6.

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Kalter-Leibovici 1991 {published data only} Kalter-Leibovici O, Van Dyk DJ, Leibovici L, Loya N, Erman A, Kremer I, et al. Risk factors for development of diabetic nephropathy and retinopathy in Jewish IDDM patients. Diabetes 1991;40(2):204-10.

Keen 2001 {published data only} Keen H, Lee ET, Russell D, Miki E, Bennett PH, Lu M. The appearance of retinopathy and progression to proliferative retinopathy: the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001;44 Suppl 2:S22-30.

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Klein 1984 {published data only} Klein BE, Davis MD, Segal P, Long JA, Harris WA, Haug GA, et al. Diabetic retinopathy. Assessment of severity and progression. Ophthalmology 1984;91(1):10-7.

Lee 1992 {published data only} Lee ET, Lee VS, Lu M, Russell D. Development of proliferative retinopathy in NIDDM: a follow-up study of American Indians in Oklahoma. Diabetes 1992;41(3):359-67.

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McCarty 2003 {published data only}

McCarty DJ, Fu CL, Harper CA, Taylor HR, McCarty CA. Fiveyear incidence of diabetic retinopathy in the Melbourne Visual Impairment Project. Clinical & Experimental Ophthalmology 2003;31(5):397-402.

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Nelson RG, Wolfe JA, Horton MB, Pettitt DJ, Bennett PH, Knowler WC. Proliferative retinopathy in NIDDM: incidence and risk factors in Pima Indians. Diabetes 1989;38(4):435-40.

Okudaira 2000 {published data only}

Okudaira M, Yokoyama H, Otani T, Uchigata Y, Iwamoto Y. Slightly elevated blood pressure as well as poor metabolic control are risk factors for the progression of retinopathy in early-onset Japanese Type 2 diabetes. Journal of Diabetes and its Complications 2000;14(5):281-7.

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Porta M, Sjoelie AK, Chaturvedi N, Stevens L, Rottiers R, Veglio M, et al. Risk factors for progression to proliferative diabetic retinopathy in the EURODIAB Prospective Complications Study. Diabetologia 2001;44(12):2203-9.

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Skrivarhaug T, Fosmark DS, Stene LC, Bangstad HJ, Sandvik L, Hanssen KF, et al. Low cumulative incidence of proliferative retinopathy in childhood-onset type 1 diabetes: a 24-year follow-up study. Diabetologia 2006;49(10):2281-90.

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Klein R, Klein BEK, Moss SE, Wong TY, Hubbard L, Cruickshanks KJ, et al. The relation of retinal vessel caliber to the incidence and progression of diabetic retinopathy: XIX: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Archives of Ophthalmology 2004;122(1):76-83.

Klein R, Klein BEK, Moss SE, Wong TY. Retinal vessel caliber and microvascular and macrovascular disease in type 2 diabetes: XXI: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Ophthalmology 2007;114(10):1884-92.

Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BEK. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology 2008;115(11):1859-68.

Klein R, Meuer SM, Moss SE, Klein BE. Retinal microaneurysm counts and 10-year progression of diabetic retinopathy. Archives of Ophthalmology 1995;113(11):1386-91.

Klein R, Meuer SM, Moss SE, Klein BE. The relationship of retinal microaneurysm counts to the 4-year progression of diabetic retinopathy. Archives of Ophthalmology 1989;107(12):1780-5.

Klein R, Moss SE, Klein BEK. Is gross proteinuria a risk factor for the Incidence of proliferative diaberic retinopathy? Ophthalmology 1993;100(8):1140-6. Moss SE, Klein R, Klein BE. Association of cigarette smoking with diabetic retinopathy. Diabetes Care 1991;14(2):119-26. Moss SE,

Klein R, Klein BE. Cigarette smoking and tenyear progression of diabetic retinopathy. Ophthalmology 1996;103(9):1438-42. Moss SE, Klein R, Klein BE. Ocular factors in the incidence and progression of diabetic retinopathy. Ophthalmology 1994;101(1):77-83.

Moss SE, Klein R, Klein BEK. The association of alcohol consumption with the incidence and progression of diabetic retinopathy. Ophthalmology 1994;101(12):1962-8.

1.1.13.2 Economic

No economic studies were included.

Appendices

Appendix A – Review protocols

Review protocol for prognostic factors for the progression of non-proliferative diabetic retinopathy in people with diabetic retinopathy to:

- **proliferative diabetic retinopathy**
- **diabetic macular oedema**
- **diabetic macular ischaemia**

ID	Field	Content
0.	PROSPERO registration number	1 CRD42022354177
1.	Review title	Q1: What are the prognostic factors for the progression of non-proliferative diabetic retinopathy in people with diabetic retinopathy
2.	Review question	What are the prognostic factors for the progression of non-proliferative diabetic retinopathy in people with diabetic retinopathy to? • proliferative diabetic retinopathy • diabetic macular oedema • diabetic macular ischaemia

3.	Objective	To determine which systemic and ocular factors that might predict progression of non-proliferative diabetic retinopathy in people with diabetic retinopathy to • proliferative diabetic retinopathy • diabetic macular oedema • diabetic macular ischaemia Progression to diabetic retinopathy will be covered by an ongoing Cochrane review: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013775/full#CD013775-sec1-0003 A systematic search will not be conducted for this aspect of the review. A systematic search will be conducted for evidence on progression to diabetic macular oedema and diabetic macular ischaemia.
4.	Searches	Progression to diabetic retinopathy will be covered by an ongoing Cochrane review: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013775/full#CD013775-sec1-0003 A systematic search will not be conducted for this aspect of the review.

		A systematic search will be conducted for evidence on progression to diabetic macular oedema and diabetic macular ischaemia. The following databases will be searched for the clinical review: • Embase • MEDLINE • Medline in Process • Medline EPub Ahead of Print For the economics review the following databases will be searched on population only: • Embase • MEDLINE • Medline in Process • Medline EPub Ahead of Print • Econlit • HTA (legacy records) • NHS EED (legacy records) • INAHTA Searches will be restricted by: • Studies reported in English • Study design prognostic filters will be applied

		• Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results • No date limit will be set unless specified by the protocol • Cost Utility (specific) and Cohort Studies for the economic search Other searches: • None identified The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for all databases will be published in the final review.
5.	Condition or domain being studied	Diabetic retinopathy, macular oedema, macular ischaemia
6.	Population	Inclusion: People with non-proliferative diabetic retinopathy

7.	Predictive factors	The review will be limited to the following predictive factors: • Age • Gender • Ethnicity • Socio-economic status • Smoking habits • presence/absence of cardiovascular disease • cerebrovascular disease • nephropathy and specifically chronic kidney failure (defined as estimated glomerular filtration rate (GFR) of < 60 mL/min/1.73 m2), • peripheral neuropathy and specifically foot ulcers, amputation • body mass index (BMI) • neck/waist circumference • glycated haemoglobin • blood pressure • cholesterol and triglyceride • Anatomical changes in the retina (for example venous beading, cotton wool spots, venous looping, intraretinal microvascular abnormality, microaneurysms, exudates, dot-blot haemorrhages, neovascularisation) • Sleep apnoea • Duration of diabetes • Learning disability or mental health issue • Pregnancy

		Note that the Cochrane review includes an exhaustive search for risk factors (not limited to those in the list above), however, for the purpose of this evidence review, only those specified in the list above will be reported.
8.	Reference standard	Progression to: - Proliferative diabetic retinopathy (treatment for diabetic retinopathy will be taken as a surrogate measure of progression). - Diabetic macular oedema (treatment for diabetic macular oedema will be taken as a surrogate measure of development of macular oedema) - Diabetic macular ischaemia
9.	Types of study to be included	- Cohort studies - Studies using longitudinal registry data Note that the Cochrane review also includes case-control studies and the control arms of RCTs. However, for the purpose of this review, only meeting the criteria specified above will be reported.
10.	Other exclusion criteria	Studies that were not reported in English

		Studies reporting univariate analyses only
11.	Context	Diabetic retinopathy is an important cause of sight loss in adults in the United Kingdom.
12.	Primary outcomes (critical outcomes)	Outcomes to be predicted: • Proliferative diabetic retinopathy • Diabetic macular oedema • Diabetic macular ischaemia • Adjusted odds ratios, risk ratios, hazard ratios will be used as a measure of association between the predictors and reference standard (outcomes to be predicted). • Only adjusted effect measures will be reported: univariate analyses will not be included. Outcomes will be reported at the latest time point reported by the study. Reporting at earlier timepoints will be considered to facilitate meta-analysis or where dropout means that earlier timepoints are associated with substantially more precision. Note that the Cochrane review will present both adjusted and unadjusted analysis and evidence from multiple timepoints, however, for the purpose of this review, only the outcomes that meet the criteria specified in this review will be reported.

13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. This review will use of the priority screening functionality within the EPPI-reviewer software. 50% of the database will be screened. Following this point, if 5% of the database is screened without finding an include based on title and abstract screening, screening will be stopped, and the remaining records excluded. These stopping criteria are considered appropriate based on the experience of the team, given this topic is a well defined clinical area with clear inclusion and exclusion criteria. As additional measure, the full database will be searched if there are a very small number of included studies (<30). 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Extracted information for the quantitative review will include:

		study type; study setting; study population and participant demographics and baseline characteristics; details of the intervention and comparator used; inclusion and exclusion criteria; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using appropriate checklists as described in Developing NICE guidelines: the manual. Risk of bias will be assessed using the QUIPS checklist.
16.	Strategy for data synthesis	Pairwise analysis will be considered when multiple studies have assessed the same predictor, taking account other factors that may have been adjusted for in the analysis. Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled odds ratio, risk ratio or hazard ratio will be calculated for dichotomous outcomes (using the generic inverse variance method) when the same predictive factor is reported for multiple studies_ Random effects models will be used, because of the prognostic nature of the review and the likely high clinical heterogeneity between studies. A modified version of GRADE will be used to assess the quality of the outcomes. Imprecision will not be assessed in the GRADE profile but will be summarised narratively in the committee discussion section of the evidence review. Outcomes using evidence from cohort studies will be rated as high quality initially and downgraded from this point. Reasons for upgrading the certainty of the evidence will also be considered.

17.	Analysis of sub-groups	Data will be presented separately for the following groups: • Pregnant women
18.	Type and method of review	☐ Intervention ☐ Diagnostic ☒ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English

20.	Country	England		
21.	Anticipated or actual start date	2022		
22.	Anticipated completion date	April 2024		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐

		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** NICE Guideline Development Team **5b Named contact e-mail** diabeticretinopathy@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and NICE Guideline Development Team		
25.	Review team members	From the Guideline development team: • Kathryn Hopkins • Ahmed Yosef • Syed Mohiuddin • Hannah Lomax • Kirsty Hounsell • Jenny Craven • Jenny Kendrick		

26.	Funding sources/sponsor	This systematic review is being completed by the Guideline development team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10160
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:

		• notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Diabetic retinopathy, prognostic factors
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Cost effectiveness searches

A broad search covering the diabetic retinopathy population was used to identify studies on cost effectiveness. The searches were run in February 2022.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude, comment or letter or editorial or historical articles or conference abstract or conference paper or "conference review" or letter or case report were applied in adherence to standard NICE practice and the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ, 309(6964), 1286.

Search filters

Cost utility

The NICE cost utility filter was applied to the search strategies in MEDLINE and Embase to identify cost-utility studies.

Hubbard W, et al. Development of a validated search filer to identify cost utility studies for NICE economic evidence reviews. NICE Information Services.

Cohort studies

For the modelling, cohort/registry terms were used from the NICE observational filter that was developed in-house.

The NICE Organisation for Economic Co-operation and Development (OECD) filter was also applied to search strategies in MEDLINE and Embase.

Ayiku, L., Hudson, T., et al (2021)The NICE OECD countries geographic search filters: Part 2 – Validation of the MEDLINE and Embase (Ovid) filters. Journal of the Medical Library Association)

Cost effectiveness search strategies

Database	Date searched	Database Platform	Database segment or version
EconLit	16/02/2022	OVID	<1886 to February 13, 2022>

Embase (filters applied: specific cost utility filter, cohort terms plus OECD filter)	16/02/2022	Ovid	<1974 to 2022 February 16>
HTA	16/02/2022	CRD	16-Feb-2022
INAHTA	16/02/2022	INAHTA	16-Feb-2022
MEDLINE (filters applied: specific cost utility filter, cohort terms plus OECD filter)	16/02/2022	Ovid	<1946 to February 16, 2022>
MEDLINE-in-Process (filters applied: specific cost utility filter, cohort terms)	16/02/2022	Ovid	<1946 to February 16, 2022>
MEDLINE Epub Ahead-of-Print (filters applied: specific cost utility filter, cohort terms)	16/02/2022	Ovid	<February 16, 2022>
NHS EED	16/02/2022	CRD	N/A

Database: EconLit

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 14
4 1 or 2 or 3 14

Database: Embase

Cost utility search:

1 diabetic retinopathy/ 45217
2 macular edema/ 5687
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 47443
4 1 or 2 or 3 65931
5 cost utility analysis/ 10912
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 26154
7 ((incremental* adj2 cost*) or ICER).tw. 26757
8 (cost adj2 utilit*).tw. 9655
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 2715
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 31906
11 (cost and (effect* or utilit*)).ti. 51363
12 or/5-11 81030
13 4 and 12 417
14 nonhuman/ not human/ 4929899
15 13 not 14 415
16 (conference abstract or conference paper or conference proceeding or "conference review").pt. 5091583
17 15 not 16 302

Cohort studies:

1 diabetic Retinopathy/ 45440
2 macular Edema/ 5828
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 47762
4 or/1-3 66388
5 cohort analysis/ 811098
6 Retrospective study/ 1206857
7 Prospective study/ 748103
8 (Cohort adj (study or studies)).tw. 380594
9 (cohort adj (analy* or regist*)).tw. 16437
10 (follow up adj (study or studies)).tw. 68508
11 longitudinal.tw. 384899
12 prospective.tw. 981024
13 retrospective.tw. 1068301
14 or/5-13 3358085
15 4 and 14 13743
16 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ 1511773
17 exp "organisation for economic co-operation and development"/ 1933
18 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or

greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ 3545238
19 european union/ 29144
20 developed country/ 34415
21 or/17-20 3576072
22 16 not 21 1373176
23 15 not 22 12938
24 limit 23 to english language 12133
25 nonhuman/ not human/ 4938000
26 24 not 25 12067
27 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 7072757
28 26 not 27 8733
29 limit 28 to dc=20120101-20220228 6467

Database: Health Technology Assessment (HTA)

1 MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES 118
2 MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES 82
3 ((diabet* adj4 (retin* or eye* or macular*))) 216
4 #1 OR #2 OR #3 245
5 * IN HTA FROM 2012 TO 2022 5598
6 #4 AND #5 26

Database: International Network of Agencies for Health Technology Assessment (INAHTA)

6 #5 AND #4 47
5 * FROM 2012 TO 2022 7610
4 #3 OR #2 OR #1 92
3 ((diabet* AND (retin* or eye* or macular*))) 84
2 "Macular Edema"[mh] 27
1 "Diabetic Retinopathy"[mh] 39

Database: Ovid MEDLINE(R)

Cost utility search:

1 Diabetic Retinopathy/ 27250
2 Macular Edema/ 8126

3 (diabet* adj4 (retin* or eye* or macular*)).tw. 29608
4 1 or 2 or 3 40314
5 Cost-Benefit Analysis/ 88398
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 13197
7 ((incremental* adj2 cost*) or ICER).tw. 13599
8 (cost adj2 utilit*).tw. 5176
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 1698
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 17986
11 (cost and (effect* or utilit*)).ti. 30223
12 or/5-11 100083
13 4 and 12 287
14 animals/ not humans/ 4924997
15 13 not 14 287

Cohort studies:

1 Diabetic Retinopathy/ 27317
2 Macular Edema/ 8133
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 29694
4 or/1-3 40407
5 exp Cohort Studies/ 2302163
6 (cohort adj (study or studies)).tw. 225137
7 (cohort adj (analy* or regist*)).tw. 8773
8 (follow up adj (study or studies)).tw. 48799
9 longitudinal.tw. 243228
10 prospective.tw. 570236
11 retrospective.tw. 546033
12 or/5-11 2652900
13 4 and 12 10289
14 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of

belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ 1201994
15 "organisation for economic co-operation and development"/ 417
16 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ 3386234
17 european union/ 17116
18 developed countries/ 21089
19 or/15-18 3401513
20 14 not 19 1115138
21 13 not 20 9710
22 limit 21 to english language 8875
23 Animals/ not Humans/ 4930479
24 22 not 23 8825
25 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 2225022
26 24 not 25 8658
27 limit 26 to ed=20120101-20220228 4813

Database: Ovid MEDLINE(R) In-Process & In-Data-Review Citations

Cost utility search:

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 335
4 1 or 2 or 3 335
5 Cost-Benefit Analysis/ 0
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 196
7 ((incremental* adj2 cost*) or ICER).tw. 177
8 (cost adj2 utilit*).tw. 74
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 29
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 242
11 (cost and (effect* or utilit*)).ti. 286
12 or/5-11 450

13 4 and 12 2
14 animals/ not humans/ 0
15 13 not 14 2

Cohort studies:

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 336
4 or/1-3 336
5 exp Cohort Studies/ 0
6 (cohort adj (study or studies)).tw. 4157
7 (cohort adj (analy* or regist*)).tw. 155
8 (follow up adj (study or studies)).tw. 263
9 longitudinal.tw. 3119
10 prospective.tw. 5190
11 retrospective.tw. 6965
12 or/5-11 15689
13 4 and 12 71
14 limit 13 to english language 71
15 limit 14 to dt=20120101-20220228 70

Database: Ovid MEDLINE(R) Epub Ahead of Print

Cost utility search:

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 585
4 1 or 2 or 3 585
5 Cost-Benefit Analysis/ 0
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 459
7 ((incremental* adj2 cost*) or ICER).tw. 395
8 (cost adj2 utilit*).tw. 195
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 59
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 625
11 (cost and (effect* or utilit*)).ti. 615
12 or/5-11 1199
13 4 and 12 9
14 animals/ not humans/ 0
15 13 not 14 9

Cohort studies:

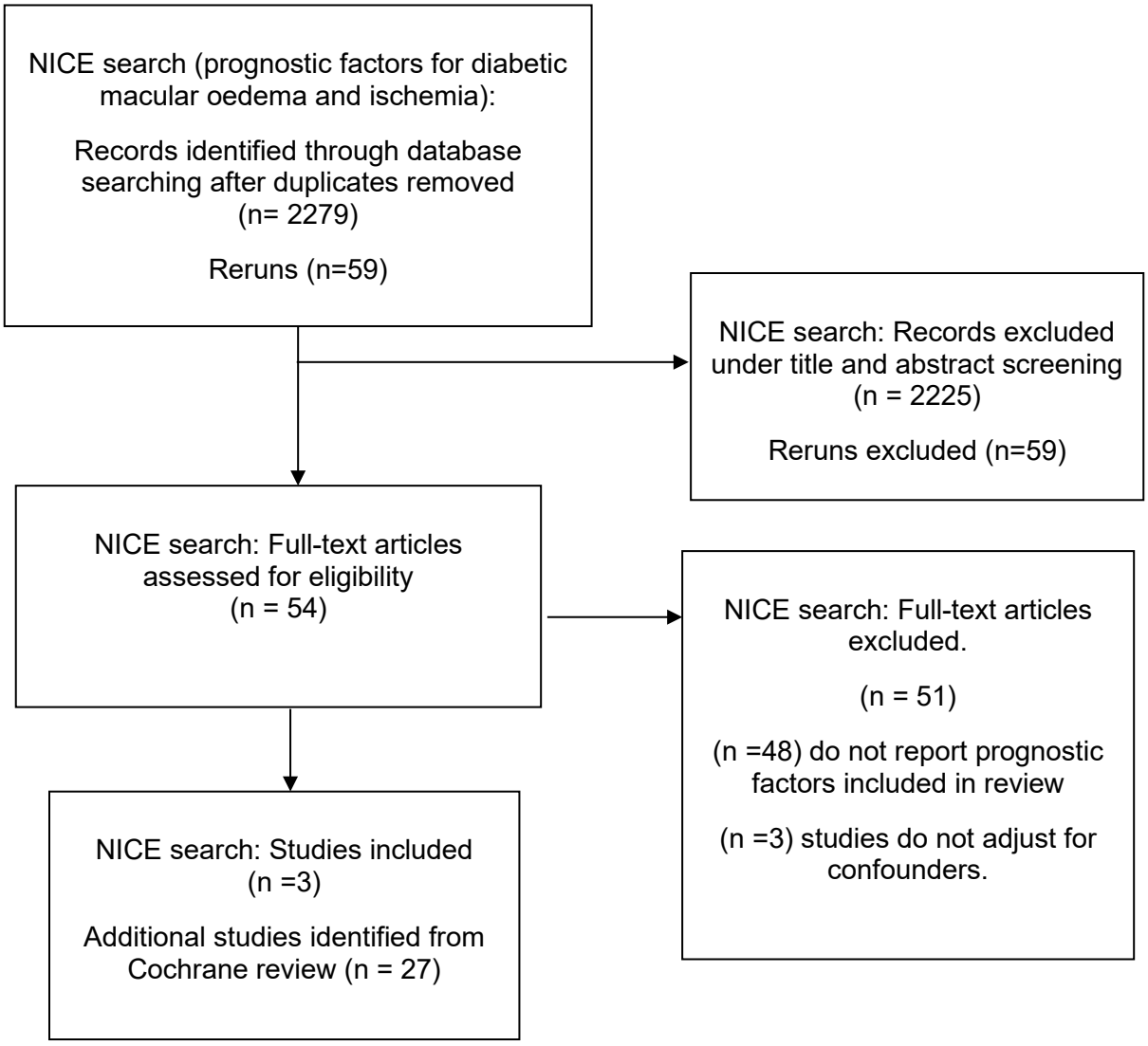
1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 563
4 or/1-3 563

5	exp Cohort Studies/	0
6	(cohort adj (study or studies)).tw.	9207
7	(cohort adj (analy* or regist*)).tw.	349
8	(follow up adj (study or studies)).tw.	607
9	longitudinal.tw.	6722
10	prospective.tw.	12241
11	retrospective.tw.	18324
12	or/5-11	37987
13	4 and 12	147
14	limit 13 to english language	147

Database: NHS Economic Evaluation Database

1	MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES	118
2	MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES	82
3	((diabet* adj4 (retin* or eye* or macular*)))	216
4	#1 OR #2 OR #3	245
5	* IN NHSEED FROM 2012 TO 2022	4897
6	#4 AND #5	19

Appendix C –Prognostic evidence study selection



Appendix D - Prognostic evidence

D.1.1 Studies included from the NICE search.

Hammes, 2015

Bibliographic Reference Hammes, H.-P.; Welp, R.; Kempe, H.-P.; Wagner, C.; Siegel, E.; Holl, R.W.; Risk factors for retinopathy and DME in type 2 diabetes-results from the German/Austrian DPV database; PLoS ONE; 2015; vol. 10 (no. 7); e0132492

Study Characteristics

Study design	Prospective cohort study
Study details	Study setting 328 diabetes centres in Germany and Austria Study dates between January 2000 and March 2013 Sources of funding This work was supported by the Kompetenznetz Diabetes mellitus (Competence Network for Diabetes mellitus) funded by the Federal Ministry of Education and Research (FKZ 01GI1106). Additional funds were provided by the European Foundation for the Study of Diabetes (EFSD).
Inclusion criteria	· Type 2 diabetes · Age at disease onset was above 40 years. · at least one retinal examination had been documented.
Exclusion criteria	younger than 40 years of age
Number of participants and recruitment methods	64784
Outcome(s) of interest	Multiple logistic regression analysis was used to evaluate relative contributions of covariates (odds ratios and 95% CI) to the risk of macular oedema
Prognostic factors or risk factors(s) or sign(s)/symptom(s)	• Age • Diabetes Duration • Gender • Hba1c • Hypertension • Smoking Some were only reported for progression to PDR and not for progression to DMO
Covariates adjusted for in the multivariable regression modelling	age, diabetes duration, gender, HbA1c, hypertension, dyslipidaemia and smoking (current and previous)

Study-level characteristics

Characteristic	**Study (N = 64784)**
Mean age (SD) Mean (SD)	68.7

Characteristic	Study (N = 64784)
The mean (SD) duration of diabetes at baseline Mean (SD)	9.2 years
DR severity at baseline	Patients by retinopathy status Mild PDR: 6646 Severe PDR: 5887 DMEP: 501

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate (incomplete retinopathy outcome reporting)
Overall risk of bias and directness	Directness	Partially applicable (included people with no retinopathy as well as people with DR)

Hsieh, 2018

Bibliographic Reference Hsieh, Yi-Ting; Tsai, Meng-Ju; Tu, Shih-Te; Hsieh, Ming-Chia; Association of Abnormal Renal Profiles and Proliferative Diabetic Retinopathy and Diabetic Macular Edema in an Asian Population With Type 2 Diabetes.; JAMA ophthalmology; 2018; vol. 136 (no. 1); 68-74

Study Characteristics

Study design	Prospective cohort study
Study details	Study location China Study setting outpatient clinic of the Metabolism Division at Changhua Christian Hospital and Kaohsiung Medical University Hospital Study dates between April 2002 and September 2004
Inclusion criteria	· Type 2 Diabetes. · Patients With Gradable Image
Exclusion criteria	Patients with ungradable image results from both eyes at baseline
Number of participants and recruitment methods	2135
Length of follow-up	8 years
Loss to follow up	37 patients were excluded because of loss of follow-up within 6 months.
Outcome(s) of interest	progression from NPDR to DMO
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Estimated Glomerular Filtration Rate (Egfr) • Body Mass Index • Systolic Blood Pressure (SBP), • Diastolic Blood Pressure • Haemoglobin A1c (Hba1c) • Fasting Glucose Level • Total Cholesterol Level

	• Triglyceride Level
Covariates adjusted for in the multivariable regression modelling	the following covariates were adjusted in the regression models using forward selection: age, sex, duration of diabetes, baseline body mass index, SBP, fasting glucose levels, HbA1c, total cholesterol levels, high-density lipoprotein cholesterol levels, low-density lipoprotein cholesterol levels, and triglyceride levels.

Study-level characteristics

Characteristic	Study (N = 2161)
Mean age (SD) Mean (SD)	63.4 (11.9)
The mean (SD) duration of diabetes at baseline Mean (SD)	15.1 (7)
DR severity at baseline	751 patients (35.2%) had NPDR, 39 (1.8%) had PDR, and 34 (1.6%) had DME

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	**Question**	**Answer**
Overall risk of bias and directness	Risk of Bias	Moderate (adjusted only for some confounding factors in multiple regression models)
Overall risk of bias and directness	Directness	Partially applicable (some people without NPDR at baseline)

Lobo, 2018

Bibliographic Reference Lobo, Conceicao; Pires, Isabel; Alves, Dalila; Pappuru, Rajeev; Ribeiro, Luisa; Cunha-Vaz, Jose; Subclinical Macular Edema as a Predictor of Progression to Central-Involved Macular Edema in Type 2 Diabetes.; Ophthalmic research; 2018; vol. 60 (no. 1); 18-22

Study Characteristics

Study design	Prospective cohort study
Study details	Study location India Study setting 2 clinical sites (AIBILI, Coimbra, Portugal, and LV-Prasad Eye Institute, Hyderabad,
Inclusion criteria	• Diabetes type 2 • aged over 35 years, • mild NPDR (levels 20–35, according (ETDRS) diabetic retinopathy severity scale) • best-corrected visual acuity (BCVA) >20/25 on the ETDRS chart • HbA1C ≤11%, with no previous treatment with laser or anti-VEGF or steroid intravitreal injection • no other retinal vascular disease or glaucoma • inadequate ocular media and/or pupil dilatation • that did not permit good-quality fundus photography.
Exclusion criteria	• Not reported

Number of participants and recruitment methods	205
Length of follow-up	24 Months
Loss to follow up	There were a total of 47 dropouts from the study (1 patient died, 11 withdrew consent, 2 had health problems, and 33 were lost to follow-up;
Outcome(s) of interest	NPDR progression to CSME and central-involved macular edema (CIME).
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender • HbA1c • Systolic Blood Pressure • Diastolic Blood Pressure • Cholesterol • Triglycerides
Covariates adjusted for in the multivariable regression modelling	multivariate logistic regressions were computed with development of CIME as the dependent variable, and RT in the CSF and in the inner and outer rings, HbA1C, cholesterol values, blood pressure values, age, and gender as independent variables.

Study-level characteristics

Characteristic	
Mean age (SD) Mean (SD)	Not reported
The mean (SD) duration of diabetes at baseline Mean (SD)	Not reported
DR severity at baseline Custom value	Not reported

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate (Unclear what variables were adjusted for in the analysis)
Overall risk of bias and directness	Directness	Directly applicable

D.1.2 Cochrane Systematic Review Perais et al-2022

Bibliographic Reference	Perais J, Agarwal R, Evans JR, Loveman E, Colquitt JL, Owens D, Hogg R, Lawrenson JG, Takwoingi Y, Lois N. Prognostic factors for the development and progression of proliferative diabetic retinopathy in people with diabetic retinopathy. Cochrane Database of Systematic Reviews 2020, Issue 11. Art. No.: CD013775

Study Characteristics

Study design	Systematic review
Study details	The date of the search was 27 May 2022.
Inclusion criteria	prospective or retrospective cohort studies, and case-control longitudinal studies, evaluating prognostic factors for the development and progression of PDR, in people who have not had previous treatment for DR (≥18 years of age) of any gender, sexual orientation, ethnicity, socioeconomic status, and geographical location, with NPDR or PDR with less than HRC-PDR, diagnosed as per standard clinical practice.
Exclusion criteria	
Prognostic Factors (s)	• Age • Gender • Ethnicity • Socio-economic status • Smoking habits • nephropathy and specifically chronic kidney failure (defined as estimated glomerular filtration rate (GFR) of < 60 mL/min/1.73 m2), • body mass index (BMI) • glycated haemoglobin • blood pressure • cholesterol and triglyceride • Anatomical changes in the retina (for example venous beading, cotton wool spots, venous looping, intraretinal microvascular abnormality, microaneurysms, exudates, dot-blot haemorrhages, neovascularisation) • Duration of diabetes
Outcome(s)	Progression to proliferative diabetic retinopathy
Number of studies included in the systematic review	59 studies
Studies from the systematic review that are relevant for use in the current review	• Nelson 1989 • Gange 2021 • Lee 2021 • Lee 2017a • Harris 2013 • Jeng 2016 • Arfken 1998 • Kalter- lei Bovici 1991

	• Portia 2001 • Gange 2021 • Lloyd 1995 • Janghor Bani 200 • Porta 2001 • Grauslund 2009a • Gui 2013 • Kim 1998 • Kim 2014 • Lee 1992 • Keen 2001 • WESDR (Klein 1994) • Roy 2006 • Klein 1984 • Skrivarhaug 2006 • Cho 2019 • Okudaira 2000 • Hseih 2018 • WESDR Moss 1994
Studies from the systematic review that are not relevant for use in the current review	• Arfken 1998 • Ballard 1986 • Bojestig 1998 • Burditt 1968 • Burgess 2015 • Chen 1995 • Dwyer 1985 • Gui 2013 • Gurreri 2019 • Hardin 1956 • Hovind 2003 • Jones 2012 • Kofoed-Enevoldsen 1987 • Kullberg 1993 • Lestradet 1981 • McCance 1989 • Miki 1969 • Nielsen 1984 • Nordwall 2015 • Pambianco 2006 • Pirart 1977 • Rodriguez-Villalobos 2005 • Rudnisky 2017 • Silva 2015 • Simonsen 1980 • Styles 2000 • Teuscher 1988 • Valone 1981 • Varma 2010 • Verdaguer 2009 • Vesteinsdottir 2010 • Voigt 2018
Additional comments	Summary details of included studies available in summary Table 1 and full evidence tables and risk of bias assessments can be found in Perais et al. 2020.

Critical appraisal - GDT Crit App - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Low *(No concerns with study eligibility criteria, search strategy, data collection or data synthesis)*
Overall study ratings	Applicability as a source of data	Directly applicable

D.1.3 Studies included from the Cochrane systematic review

For full evidence tables for the studies included from the Cochrane review, see the section on Characteristics of included studies in Perais et al. 2020.

Appendix E – GRADE tables

E.1.1.1 Prognostic evidence for people progressing to proliferative diabetic retinopathy.

The quality assessment for prognostic factors for people progressing to proliferative diabetic retinopathy can be seen in the Cochrane review (Perais et al. 2020).

E.1.1.2 Prognostic evidence for people progressing to diabetic macular oedema.

Table 27: Gender - Studies undertaking multivariable regression analyses to determine the effect of gender on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Quality
Type 2 diabetes (Male vs female)						
(OR) >1 indicates risk factor of progression to DMO at 2 years						
1 (Lobo, 2018)	205	Adjusted OR 4.09 (1.06–15.79)[1]	serious [2]	No serious	N/A	Moderate
1 Multivariate analysis but no information on what was adjusted for. 2 Moderate risk of bias 3 Single study						

Table 28: HbA1c -Studies undertaking multivariable regression analyses to determine the effect of HbA1c on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Quality
Type 2 diabetes HbA1c>8% OR >1 indicates risk factor of progression to DMO						
1 (Hammes, 2015)	64784	Adjusted OR 1.57 (1.288-1.903)[1]	serious [3]	serious[5]	N/A	Low
HbA1c at 2 years follow up						
1 (Lobo 2018)	205	Adjusted OR 0.56 (0.35–0.90)[2]	serious [3]	No serious	N/A	Moderate
1 Adjusted for age, diabetes duration, gender, HbA1c, hypertension, dyslipidaemia and smoking (current and previous) 2 Multivariate analysis but no information on what was adjusted for 3 moderate risk of bias						

No. of studies	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Quality
4 single study 5 study had a mixed population. Partially applicable to this review						

Table 29: Diastolic blood pressure -Studies undertaking multivariable regression analyses to determine the effect of diastolic blood pressure on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Quality
Type 2 diabetes- Diastolic blood pressure (OR) >1 indicates risk factor of progression to DMO						
1 (Lobo 2018)	205	Adjusted OR 1.03 (0.95–1.12)[1]	serious [2]	No serious	N/A	Moderate
1 Multivariate analysis but no information on what was adjusted for. 2 moderate risks of bias 3 single study						

Table 30: Systolic blood pressure -Studies undertaking multivariable regression analyses to determine the effect of systolic blood pressure on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Quality
Type 2 diabetes Systolic blood pressure: (OR) >1 indicates risk factor of progression to DMO						
1 (Lobo 2018)	207	Adjusted OR 0.96 0.92–1.01[1]	serious[2]	No serious	N/A	Moderate
1 Multivariate analysis but no information on what was adjusted for 2 moderate risk of bias 3 single study						

Table 31: Total cholesterol -Studies undertaking multivariable regression analyses to determine the effect of total cholesterol on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Quality
Type 2 diabetes Total cholesterol, mmol/L						
1 (Lobo 2018)	205	Adjusted OR (0.98 0.95–1.01) [1]	serious[2]	No serious	N/A	Moderate

1 Multivariate analysis but no information on what was adjusted for
2 Moderate risk of bias
3 Single study

Table 32: Triglycerides -Studies undertaking multivariable regression analyses to determine the effect of triglycerides on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Quality
Type 2 diabetes Triglycerides (OR) >1 indicates risk factor of progression to DMO						
1 (Lobo 2018)	205	Adjusted OR 1.00 (1.00–1.01)[1]	serious[2]	No serious	N/A	Moderate

1 Multivariate analysis but no information on what was adjusted for
2 moderate risk of bias
3 single study

Table 33: Estimated glomerular filtration rate (eGFR) -Studies undertaking multivariable regression analyses to determine the effect of eGFR on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Quality
Type 2 diabetes (HR) >1 indicates risk factor of progression to DMO reference standard >90 eGFR, mL/min/1.73m2						
61-90 eGFR, mL/min/1.73m2						
1 (Hsieh 2018)	1055	Adjusted HR 1.226 (0.711-2.115)[1]	serious[2]	serious[4]	N/A	Low

No. of studies	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Quality
46-60 eGFR, mL/min/1.73m						
1 (Hsieh 2018)	418	Adjusted HR 1.218 (0.559-2.654)[1]	serious[2]	serious[4]	N/A	Low
30-45 eGFR, mL/min/1.73m2						
1 (Hsieh 2018)	248	Adjusted HR 3.106 (1.268-7.609)[1]	serious[2]	serious[4]	N/A	Low
<30 eGFR, mL/min/1.73m2						
1 (Hsieh 2018)	98	Adjusted HR 1.849 (0.568-6.025)[1]	serious[2]	serious[4]	N/A	Low

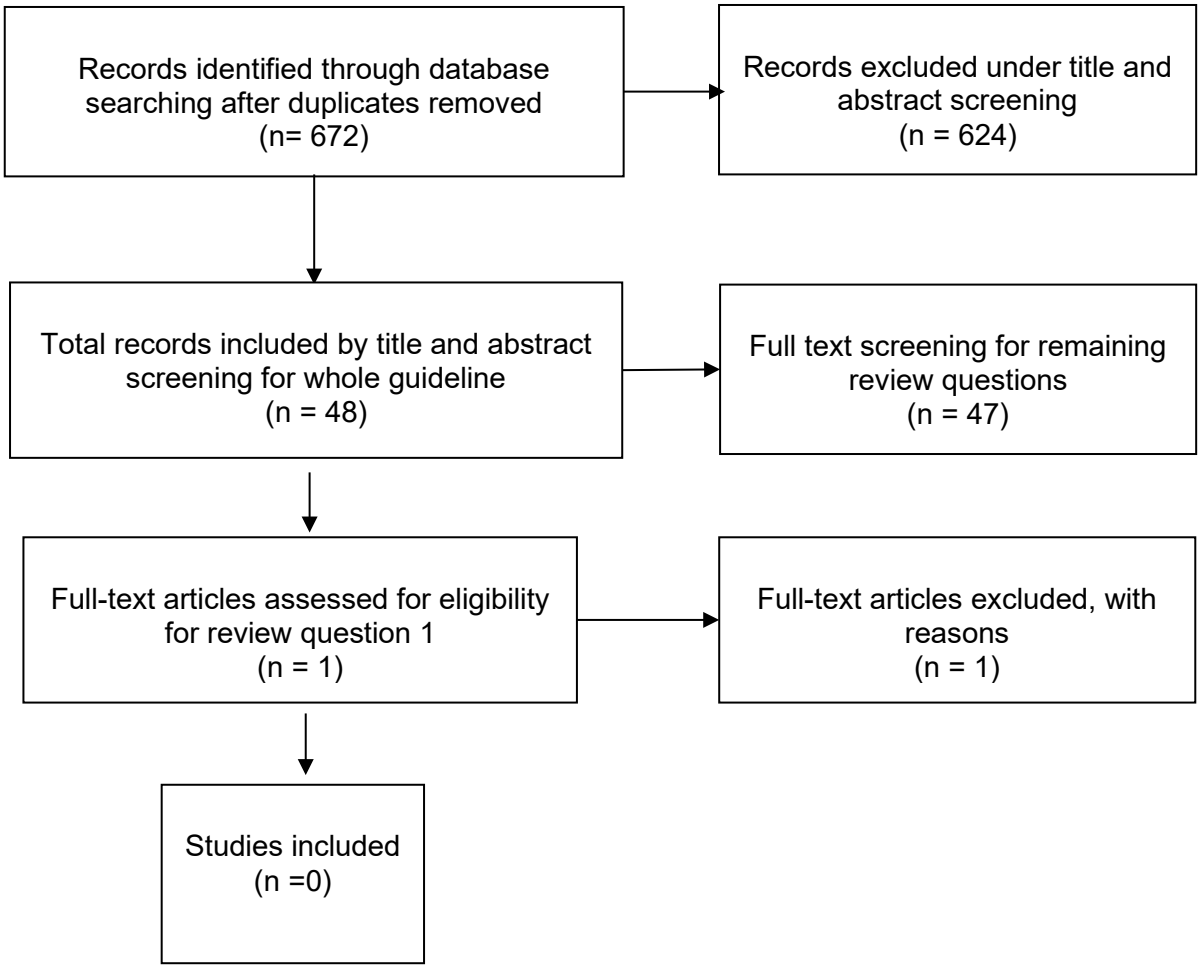
1 adjusted for age, sex, duration of diabetes, baseline body mass index, SBP, fasting glucose levels, HbA1c, total cholesterol levels, high-density lipoprotein cholesterol levels, low-density lipoprotein cholesterol levels, and triglyceride levels.
2 moderate risk of bias
3 single study
4 study had a mixed population. Partially applicable to this review

Table 34: Hypertension-Studies undertaking multivariable regression analyses to determine the effect of hypertension on progression to macular oedema.

No. of studies	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Quality
Type 2 diabetes Hypotension (>140/80 mmHg) OR >1 indicates risk factor of hypertension on progression to macular oedema.						
1 (Hammes, 2015)	64784	Adjusted OR 1.39 (1.11–1.74)[1]	serious[2]	Serious[4]	N/A	Low

1 Adjusted for age, diabetes duration, gender, HbA1c, hypertension, dyslipidaemia, and smoking (current and previous)
2 moderate risk of bias
3 single study
4 study had a mixed population. Partially applicable to this review

Appendix F – Economic evidence study selection



Appendix G – Economic evidence tables

There are no included studies for this review question.

Appendix H – Health economic model

Original health economic modelling has not been conducted for this review question.

Appendix I – Excluded studies

Clinical evidence

Study	Reason for exclusion
Agarwal, M., Sachdeva, M., Shah, S. et al. (2022) Correlating the patterns of diabetic macular edema, optical coherence tomography biomarkers and grade of diabetic retinopathy with stage of renal disease. International Ophthalmology 42(11): 3333-3343	- measuring progression to PDR
Allen, D.W., Liew, G., Cho, Y.H. et al. (2022) Thirty-Year Time Trends in Diabetic Retinopathy and Macular Edema in Youth With Type 1 Diabetes. Diabetes Care 45(10): 2247-2254	- Prevalence study
Arulanandham, A., Raju, A., Pradeep Rajkumar, L.A. et al. (2012) Prevalence of clinically significant macular edema [CSME] among glitazone users and non- users of type-2 DM patients with diabetic retinopathy. International Journal of Drug Development and Research 4(2): 132-137	- Prevalence study
Bailey, C C, Sparrow, J M, Grey, R H et al. (1999) The National Diabetic Retinopathy Laser Treatment Audit. III. Clinical outcomes. Eye (London, England) 13 (Pt 2): 151-9	- End point measuring progression to PDR
Bertelsen, Geir, Peto, Tunde, Lindekleiv, Haakon et al. (2013) Tromso eye study: prevalence and risk factors of diabetic retinopathy. Acta ophthalmologica 91(8): 716-21	- End point measuring progression to PDR
Burgess, P.I., MacCormick, I.J.C., Harding, S.P. et al. (2013) Epidemiology of diabetic retinopathy and maculopathy in Africa: A systematic review. Diabetic Medicine 30(4): 399-412	- a systematic review used to crosscheck studies
Burnett, Anthea, Lee, Ling, D'Esposito, Fabrizio et al. (2019) Rapid assessment of avoidable blindness and diabetic retinopathy in people aged 50 years and older in the National Capital District of Papua New Guinea. The British journal of ophthalmology 103(6): 743-747	- End point measuring progression to PDR
Busch, C., Katzmann, J.L., Jochmann, C. et al. (2021) General health of patients with diabetic macular edema-The LIPSIA study. PLoS ONE 16(6june2021): e0252321	wrong study design: narrative review
Chung, Yoo-Ri, Park, Sung Wook, Choi, Shin-Young et al. (2017) Association of statin use and hypertriglyceridemia with diabetic macular edema in patients with type 2 diabetes and diabetic retinopathy. Cardiovascular diabetology 16(1): 4	none of the prognostic factors reported match review.
Creuzot-Garcher, C., Massin, P., Srour, M. et al. (2022) Epidemiology of Treated Diabetes Ocular	- Narrative review

Study	Reason for exclusion
Complications in France 2008-2018-The LANDSCAPE French Nationwide Study. Pharmaceutics 14(11): 2330	
Crosby-Nwaobi, Roxanne, Chatziralli, Irini, Sergentanis, Theodoros et al. (2015) Cross Talk between Lipid Metabolism and Inflammatory Markers in Patients with Diabetic Retinopathy. Journal of diabetes research 2015: 191382	- End point measuring progression to PDR
Das, Anthony Vipin, Prashanthi, Gumpili Sai, Das, Taraprasad et al. (2021) Clinical profile and magnitude of diabetic retinopathy: An electronic medical record-driven big data analytics from an eye care network in India. Indian journal of ophthalmology 69(11): 3110-3117	- End point measuring progression to PDR
Das, Radha, Kerr, Rebecca, Chakravarthy, Usha et al. (2015) Dyslipidemia and Diabetic Macular Edema: A Systematic Review and Meta-Analysis. Ophthalmology 122(9): 1820-7	- none of the prognostic factors reported match review protocol
Fairchild, J M, Hing, S J, Donaghue, K C et al. (1994) Prevalence and risk factors for retinopathy in adolescents with type 1 diabetes. The Medical journal of Australia 160(12): 757-62	- measuring prevalence of PDR
Henricsson, M, Sellman, A, Tyrberg, M et al. (1999) Progression to proliferative retinopathy and macular oedema requiring treatment. Assessment of the alternative classification of the Wisconsin Study. Acta ophthalmologica Scandinavica 77(2): 218-23	- mixed population of PDR and DMO
Hirai, Flavio E, Knudtson, Michael D, Klein, Barbara E K et al. (2008) Clinically significant macular edema and survival in type 1 and type 2 diabetes. American journal of ophthalmology 145(4): 700-6	- measuring progression to PDR
Jones, Colin D, Greenwood, Richard H, Misra, Aseema et al. (2012) Incidence and progression of diabetic retinopathy during 17 years of a population-based screening program in England. Diabetes care 35(3): 592-6	- Mixed population
Kaba, Q., Tai, F., Al-Awadi, A. et al. (2022) Examining the Relationship Between Diabetic Macular Edema, and Obstructive Sleep Apnea. Clinical Ophthalmology 16: 1215-1223	Association study
Klein, R, Klein, B E, Moss, S E et al. (1994) Relationship of hyperglycemia to the long-term incidence and progression of diabetic retinopathy. Archives of internal medicine 154(19): 2169-78	- End point measuring progression to PDR
Klein, R, Klein, B E, Moss, S E et al. (1994) The Wisconsin Epidemiologic Study of diabetic retinopathy. XIV. Ten-year incidence and progression of diabetic retinopathy. Archives of ophthalmology (Chicago, Ill. : 1960) 112(9): 1217-28	- End point measuring progression to PDR

Study	Reason for exclusion
Leese, G. (2004) Longitudinal study examining the risk factors for proliferative retinopathy and maculopathy in type-I diabetes: The Royal College of Physicians of Edinburgh Diabetes Register Group. Eye 18(8): 814-820	Cross sectional study
Leong, W.B., Jadhakhan, F., Taheri, S. et al. (2016) Effect of obstructive sleep apnoea on diabetic retinopathy and maculopathy: A systematic review and meta-analysis. Diabetic Medicine 33(2): 158-168	- a systematic review used to check for primary studies
Li, Z., Liu, R., Xiao, O. et al. (2019) Progression of myopic maculopathy in highly myopic chinese eyes. Investigative Ophthalmology and Visual Science 60(4): 1096-1104	- wrong population
Lim, Laurence Shen, Tai, E Shyong, Mitchell, Paul et al. (2010) C-reactive protein, body mass index, and diabetic retinopathy. Investigative ophthalmology & visual science 51(9): 4458-63	Cross sectional study
Lloyd, C E, Klein, R, Maser, R E et al. (1995) The progression of retinopathy over 2 years: the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study. Journal of diabetes and its complications 9(3): 140-8	- End point measuring progression to PDR
Lobo, C., Santos, T., Marques, I.P. et al. (2022) Characterisation of progression of macular oedema in the initial stages of diabetic retinopathy: a 3-year longitudinal study. Eye (Basingstoke)	- end point not measuring prognostic factors
Marques, I.P., Ribeiro, M.L., Santos, T.P. et al. (2022) Different Risk Profiles for Progression of Nonproliferative Diabetic Retinopathy: A 2-Year Study. Ophthalmology and Therapy	- End point measuring progression to PDR
Martin-Merino, E, Fortuny, J, Rivero-Ferrer, E et al. (2017) Risk factors for diabetic macular oedema in type 2 diabetes: A case-control study in a United Kingdom primary care setting. Primary care diabetes 11(3): 288-296	- no multivariate analysis conducted
Moss, S E; Klein, R; Klein, B E (1994) Ocular factors in the incidence and progression of diabetic retinopathy. Ophthalmology 101(1): 77-83	- End point measuring progression to PDR
Moss, S E; Klein, R; Klein, B E (1994) Ten-year incidence of visual loss in a diabetic population. Ophthalmology 101(6): 1061-70	- End point do not match that specified in the protocol
Nguyen, H T, Luzio, S D, Dolben, J et al. (1996) Dominant risk factors for retinopathy at clinical diagnosis in patients with type II diabetes mellitus. Journal of diabetes and its complications 10(4): 211-9	- End point measuring progression to PDR
Panozzo, G., Mura, G.D., Franzolin, E. et al. (2022) Early DMO: a predictor of poor outcomes following cataract surgery in diabetic patients. The DICAT-II study. Eye (Basingstoke) 36(8): 1687-1693	- End point do not match that specified in the protocol

Study	Reason for exclusion
Pires, Isabel, Santos, Ana Rita, Nunes, Sandrina et al. (2013) Subclinical macular edema as a predictor of progression to clinically significant macular edema in type 2 diabetes. Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde 230(4): 201-6	- prognostic factor does not match review protocol
Radwan, Salma H, Soliman, Ahmed Z, Tokarev, Julian et al. (2015) Association of Disorganization of Retinal Inner Layers With Vision After Resolution of Center-Involved Diabetic Macular Edema. JAMA ophthalmology 133(7): 820-5	- End point measuring progression to PDR
Rajalakshmi, Ramachandran, Amutha, Anandakumar, Ranjani, Harish et al. (2014) Prevalence and risk factors for diabetic retinopathy in Asian Indians with young onset type 1 and type 2 diabetes. Journal of diabetes and its complications 28(3): 291-7	- End point measuring progression to PDR
Raum, Philipp, Lamparter, Julia, Ponto, Katharina A et al. (2015) Prevalence and Cardiovascular Associations of Diabetic Retinopathy and Maculopathy: Results from the Gutenberg Health Study. PloS one 10(6): e0127188	- End point measuring progression to PDR
Schreur, Vivian, van Asten, Freekje, Ng, Heijan et al. (2018) Risk factors for development and progression of diabetic retinopathy in Dutch patients with type 1 diabetes mellitus. Acta ophthalmologica 96(5): 459-464	- End point measuring progression to PDR
Shah, S P, Patel, M, Thomas, D et al. (2006) Factors predicting outcome of vitrectomy for diabetic macular oedema: results of a prospective study. The British journal of ophthalmology 90(1): 33-6	- population does not match protocol
Shalchi, Zaid, Okada, Mali, Bruynseels, Alice et al. (2018) Effect of glycosylated hemoglobin on response to ranibizumab therapy in diabetic macular edema: real-world outcomes in 312 patients. Canadian journal of ophthalmology. Journal canadien d'ophtalmologie 53(4): 415-419	- wrong intervention
Singh, Harsh V, Das, Shubhra, Deka, Dipali C et al. (2021) Prevalence of diabetic retinopathy in self-reported diabetics among various ethnic groups and associated risk factors in North-East India: A hospital-based study. Indian journal of ophthalmology 69(11): 3132-3137	- prevalence
Sun, Jennifer K, Lin, Michael M, Lammer, Jan et al. (2014) Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. JAMA ophthalmology 132(11): 1309-16	wrong intervention/ outcome measurement
Sun, Zihan, Tang, Fangyao, Wong, Raymond et al. (2019) OCT Angiography Metrics Predict Progression	- outcome/End point do not match that specified in the protocol

Study	Reason for exclusion
of Diabetic Retinopathy and Development of Diabetic Macular Edema: A Prospective Study. Ophthalmology 126(12): 1675-1684	Mixed population
Syriga, Maria, Ioannou, Zina, Pitsas, Christos et al. (2022) Diabetic retinopathy in Greece: prevalence and risk factors studied in the medical retina clinic of a Greek tertiary hospital. International ophthalmology 42(6): 1679-1687	- End point do not match that specified in the protocol Prevalence study
Terada, Noriko, Murakami, Tomoaki, Uji, Akihito et al. (2020) Hyperreflective Walls in Foveal Cystoid Spaces as a Biomarker of Diabetic Macular Edema Refractory to Anti-VEGF Treatment. Scientific reports 10(1): 7299	- End point do not match that specified in the protocol Wrong intervention/ outcome measure
Vujosevic, Stela, Pucci, Porzia, Casciano, Margherita et al. (2017) A decade-long telemedicine screening program for diabetic retinopathy in the north-east of Italy. Journal of diabetes and its complications 31(8): 1348-1353	- End point do not match that specified in the protocol Wrong population
Wang, Yu T, Tadarati, Mongkol, Wolfson, Yulia et al. (2016) Comparison of Prevalence of Diabetic Macular Edema Based on Monocular Fundus Photography vs Optical Coherence Tomography. JAMA ophthalmology 134(2): 222-8	- End point do not match that specified in the protocol Wrong outcome measurement
Wang, Yu, Lin, Zhong, Zhai, Gang et al. (2022) Prevalence of and Risk Factors for Diabetic Retinopathy and Diabetic Macular Edema in Patients with Early- and Late-Onset Diabetes Mellitus. Ophthalmic research 65(3): 293-299	- End point do not match that specified in the protocol Mixed population
Zander, E, Herfurth, S, Bohl, B et al. (2000) Maculopathy in patients with diabetes mellitus type 1 and type 2: associations with risk factors. The British journal of ophthalmology 84(8): 871-6	Cross sectional study
Zhang, Jun, Ma, Jingxue, Zhou, Nalei et al. (2015) Insulin use and risk of diabetic macular edema in diabetes mellitus: a systemic review and meta-analysis of observational studies. Medical science monitor : international medical journal of experimental and clinical research 21: 929-36	- End point do not match that specified in the protocol Systematic review used to check for primary studies
Zhu, Z., Cheng, W., Bulloch, G. et al. (2022) Choriocapillaris flow deficit as a biomarker for diabetic retinopathy and diabetic macular edema: 3-year longitudinal cohort: Choriocapillaris flow predicts DR progression and DME development. American journal of ophthalmology	- End point do not match that specified in the protocol Prognostic factor not included in review protocol
Zhuang, Xuenan, Cao, Dan, Yang, Dawei et al. (2019) Association of diabetic retinopathy and diabetic macular oedema with renal function in southern Chinese patients with type 2 diabetes mellitus: a single-centre observational study. BMJ open 9(9): e031194	Cross sectional study

Economic evidence

Title	Reason for exclusion
Olson, J, Sharp, P, Goatman, K et al. (2013) Improving the economic value of photographic screening for optical coherence tomography-detectable macular oedema: a prospective, multicentre, UK study. Health technology assessment (Winchester, England) 17(51): 1-142	Not applicable - not comparing prognostic factors

Appendix J – Research recommendations – full details

J.1.1 Research recommendation

J.1.2 What are the prognostic factors for the progression of non proliferative diabetic retinopathy to proliferative diabetic retinopathy, diabetic macular oedema and macular ischemia?

J.1.3 Why this is important.

Progression of non-proliferative diabetic retinopathy to proliferative diabetic retinopathy, diabetic macular oedema or diabetic macular ischemia can have negative consequences for people with diabetes. Progression also results in people needing more treatments, which impacts on both patients and the NHS. Some studies have considered the risk factors for progression of non-proliferative diabetic retinopathy, but there is limited high-quality evidence to help determine which factors are the biggest risk for progression. It is important to identify which factors, or combination of factors, are accurate indicators of disease progression and can be used in clinical practice in decision-making.

J.1.4 Rationale for research recommendation

Importance to 'patients' or the population	A greater awareness of the risk factors for progressing from non-proliferative diabetic retinopathy will help people be more aware of when they are at risk of progressing. This may help people to modify some risk factors to reduce their risk of progressing. It will also help those who are most at risk be given the appropriate monitoring and follow-up.
Relevance to NICE guidance	Prognostic factors have been considered in this guideline and there is a lack of data on several prognostic factors for people with non-proliferative diabetic retinopathy. More high quality information on risk factors will help with the development of recommendations in future guideline updates.
Relevance to the NHS	Knowledge of the main prognostic factors would affect the types of treatment and monitoring frequency for people with non-proliferative diabetic retinopathy who are likely to progress to proliferative diabetic retinopathy, diabetic macular oedema or diabetic macular ischemia. It may also predict future healthcare needs for treatment
National priorities	Moderate
Current evidence base	41 studies for progression to proliferative diabetic retinopathy and 3 studies for progression to diabetic macular oedema. Current evidence is low quality. There is no evidence for progression to diabetic macular ischemia.
Equality considerations	None known

J.1.5 Modified PICO table.

Population	People with non-proliferative diabetic retinopathy
Prognostic factors	• Age • Gender • Ethnicity • Socio-economic status • Smoking habits • presence/absence of cardiovascular disease • cerebrovascular disease • nephropathy and specifically chronic kidney failure (defined as estimated glomerular filtration rate (GFR) of < 60 mL/min/1.73 m2), • peripheral neuropathy and specifically foot ulcers, amputation • body mass index (BMI) • neck/waist circumference • glycated haemoglobin • blood pressure • cholesterol and triglyceride • Anatomical changes in the retina (for example venous beading, cotton wool spots, venous looping, intraretinal microvascular abnormality, microaneurysms, exudates, dot-blot haemorrhages, neovascularisation) • Sleep apnoea • Duration of diabetes • Learning disability or mental health issue • Pregnancy
Reference standard	Progression to: • Proliferative diabetic retinopathy • Diabetic macular oedema • Diabetic macular ischaemia
Outcome	• Adjusted odds ratios, risk ratios, hazard ratios
Study design	• Cohort studies • Studies using longitudinal registry data
Timeframe	Long term (20 years)
Additional information	None