



This is a peer-reviewed, final published version of the following document and is licensed under Creative Commons: Attribution-Noncommercial-No Derivative Works 4.0 license:

**Scanlon, Peter H ORCID logoORCID: <https://orcid.org/0000-0001-8513-710X> (2022) Improving the screening of risk factors in diabetic retinopathy. Expert Review of Endocrinology and Metabolism, 17 (3). pp. 235-243. doi:10.1080/17446651.2022.2078305**

Official URL: <http://doi.org/10.1080/17446651.2022.2078305>

DOI: <http://dx.doi.org/10.1080/17446651.2022.2078305>

EPrint URI: <https://eprints.glos.ac.uk/id/eprint/11262>

#### **Disclaimer**

The University of Gloucestershire has obtained warranties from all depositors as to their title in the material deposited and as to their right to deposit such material.

The University of Gloucestershire makes no representation or warranties of commercial utility, title, or fitness for a particular purpose or any other warranty, express or implied in respect of any material deposited.

The University of Gloucestershire makes no representation that the use of the materials will not infringe any patent, copyright, trademark or other property or proprietary rights.

The University of Gloucestershire accepts no liability for any infringement of intellectual property rights in any material deposited but will remove such material from public view pending investigation in the event of an allegation of any such infringement.

PLEASE SCROLL DOWN FOR TEXT.



## Improving the screening of risk factors in diabetic retinopathy

Peter H Scanlon

To cite this article: Peter H Scanlon (2022) Improving the screening of risk factors in diabetic retinopathy, Expert Review of Endocrinology & Metabolism, 17:3, 235-243, DOI: [10.1080/17446651.2022.2078305](https://doi.org/10.1080/17446651.2022.2078305)

To link to this article: <https://doi.org/10.1080/17446651.2022.2078305>



© 2022 Informa UK Limited, trading as Taylor & Francis Group



Published online: 22 Jun 2022.



Submit your article to this journal [↗](#)



Article views: 105



View related articles [↗](#)



View Crossmark data [↗](#)

REVIEW



## Improving the screening of risk factors in diabetic retinopathy

Peter H Scanlon<sup>a,b,c,d</sup>

<sup>a</sup>Consultant Ophthalmologist, Department of Ophthalmologist, Gloucestershire Hospitals NHS Foundation Trust Cheltenham, UK; <sup>b</sup>National Clinical Lead, NHS Diabetic Eye Screening Programme (Ophthalmology), Public Health Commissioning and Operations, England; <sup>c</sup>Associate Professor, Nuffield Department of Clinical Neuroscience, University of Oxford, UK; <sup>d</sup>Visiting Professor, School of Health and Social Care, University of Gloucestershire, UK

### ABSTRACT

**Introduction:** In 2002, Diabetic Retinopathy was reported as the leading cause of blindness in the working age group. The introduction of systematic screening programs in the UK has reduced visual loss and blindness due to diabetic retinopathy, but it does still occur with catastrophic consequences for the individual.

**Areas covered:** The author conducted an ongoing search for articles relating to diabetic retinopathy since 2000 utilizing Zetoc Alert with keywords and contents page lists from relevant journals. This review covers the risk factors for loss of vision due to diabetic retinopathy and discusses ways in which the awareness of these risk factors can be used to further reduce visual loss. Some risk factors such as glycemic and B/P control are well known from landmark trials. This review has included these factors but concentrated more on the evidence behind those risk factors that are not so clearly defined or so well known.

**Expert opinion:** The major risk factors are well known, but one continues to find that people with diabetes lose vision in situations in which a better awareness of the risks by both the individual with diabetes and the health workers involved may have prevented the visual loss.

### ARTICLE HISTORY

Received 5 February 2022  
Accepted 12 May 2022

### KEYWORDS

Diabetic retinopathy;  
diabetic macular edema; risk  
factors; screening; visual loss

## 1. Introduction

### 1.1. Importance of diabetic retinopathy

Kocur [1] reported in 2002 that, in people of working age in Europe, diabetic retinopathy was the most frequently reported causes of serious visual loss and blindness. Since that time strenuous efforts have been made to reduce the numbers who lose vision due to diabetic retinopathy and systematic screening programs have developed in the UK. In 2012, Sivaprasad [2] reported that minority ethnic communities with type 2 diabetes of African/Afro-Caribbean's and South Asian origin in the UK are more prone to visual impairment than white Europeans

In 2014, Liew [3] reported that diabetic retinopathy/maculopathy was no longer the leading cause of certifiable blindness among working age adults in England and there have been further reports [4,5] of reductions in blindness.

### 1.2. Methodology

The author has conducted an ongoing search for articles relating to diabetic retinopathy since March 2000. This involves a search technique for articles relating to diabetic retinopathy utilizing Zetoc Alert (<http://zetoc.jisc.ac.uk/>). This enables a search of the British Library's electronic table of contents on a daily basis using 22 different combinations of keywords (e.g. 'retinopathy' or 'surveillance' & 'diabet' &

'retinopathy' in title) on a daily basis. Page lists from 22 journals are also reviewed monthly. Articles of interest identified in his way are found from on-line electronic journal resources (e.g. Open Athens [6] or the Royal Society of Medicine [7]). This review identified all articles linked to the question 'What risk factors are there for diabetic retinopathy and progression to sight threatening diabetic retinopathy?'

## 2. Body of the article

### 2.1. Risk factors for progression of diabetic retinopathy

Many of the early studies which identified the main risk factors for progression of diabetic retinopathy (DR) to sight threatening diabetic retinopathy (STDR) were reported at a time when glycemic and blood pressure (B/P) control were poor and the prevalence of diabetic retinopathy and proliferative diabetic retinopathy was high. In 1980, baseline data from a population with diabetes in Wisconsin [8,9] reported a high prevalence of diabetic retinopathy (DR) and proliferative diabetic retinopathy (PDR). The 4-yr incidence figures reported in 1989 from the same population for any DR and PDR in those aged <30 yrs taking insulin were found to be 59% and 10.5%, in those ≥30 yrs taking insulin 47.4% and 7.4%, and in those aged ≥30 yrs not taking insulin 34.4% and 2.3%. A recent study [10] from Gloucestershire (92.5% Type 2, 7.2% Type 1, and 0.3% 'Other' Type of diabetes), reported the 4 year incidence

**Article highlights**

When trying to further reduce vision loss and blindness it will be important for clinicians to:

- Have an awareness of all the situations in which the risk of diabetic retinopathy progression is more likely
- Work collaboratively with other disciplines to try and reduce visual loss
- Assist with linkage of data so that the risk factor data can be used for the benefit of the person with diabetes

of any DR was 40.3 (95% CI: 39.1, 41.5) and PDR 1.2% (95% CI: 1.1, 1.4) with increased incidence of PDR in those with more severe retinopathy at baseline. In 2014, Broe reported [11] the 16-yr incidence of PDR in Type 1 diabetes was 31%. Wong [12], Klein [13], and Kiire [14] reported lower rates of progression from no DR to STDR and Visual Loss in later time periods, which is likely to be due to better control of risk factors that were identified in the early studies.

The following risk factors were identified:

**2.1.1. The current level of retinopathy in an eye**

The Early Treatment Diabetic Retinopathy Study [15] (ETDRS) described the progression of diabetic retinopathy in relation to the development of the specific lesions and later reported the ETDRS severity scale [16] which reported the risk of progression to PDR based on lesions in seven 30 degree stereo photographic fields taken in the study. However, Wong [12] reported that ETDRS levels were only reported in 4% of studies in his review. Wilkinson et al. developed a simplified International classification in which the highest risk of developing proliferative retinopathy was defined by the ETDRS '4:2:1 rule,' defining severe non-proliferative DR as:

- a) Extensive intraretinal (blot) hemorrhages (>20) in 4 quadrants or
- b) Definite venous beading in 2+ quadrants or
- c) Prominent intraretinal microvascular abnormalities (IRMA) in 1+ quadrant and no signs of PDR

Aldington [17] first reported a relationship between the retinal microaneurysm count and progression of diabetic retinopathy, which was confirmed in further studies [18,19]. Scanlon reported [20] a lower rate of progression if diabetic retinopathy was only present in one eye than if it was present in both eyes.

**2.1.2. Glycemic control**

Landmark clinical trials such as the Diabetes Control and Complications Trial [21,22], the United Kingdom Prospective Diabetes Study [23,24] and the Wisconsin Epidemiological Study [25,26] have shown the importance of glycemic control. The only word of caution with respect to glycemic control was from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial which was designed to examine the effects of intensive glycemic control on cardiovascular events in persons with type 2 diabetes who were at high risk for such events but

this intervention was stopped early [27] because of the effects of this intervention on mortality.

**2.1.3. The early worsening phenomenon [28]**

In the Diabetes Control and Complications Trial, early worsening of retinopathy was seen in 13.1% of those in the intensive treatment group and only 7.6% of those in the conventional treatment group. However, in those with early worsening who had received intensive treatment, the long-term outcomes were similar to or better than those conventionally treated.

Patients who are prone to this phenomenon are those people with uncontrolled type 1 or 2 diabetes who are treated more intensively (e.g. Type 2 started on insulin [29] or Type 1 treated more intensively in pregnancy [30–32]), and after pancreas transplantation [33] or bariatric surgery [34]. A review [35] described early worsening as developing in 10–20% of patients within 3–6 months after abrupt improvement of glucose control, and in nearly two times that proportion in patients with advanced baseline diabetic retinopathy (DR).

**2.1.4. Systemic hypertension [36,37]**

In 1992, a study [36] of 600 patients with Type 1 diabetes in Norway, in a multiple logistic regression model, found mean arterial blood pressure to be significantly associated with retinopathy. The importance of control of systolic and diastolic B/P in reducing the development of STDR and Diabetic Macular Edema (DMO) was also found in Wisconsin Epidemiological Study [25,26] and in the UKPDS study [37,38]. More recently, the ACCORD [39] and the ADVANCE [40] trials did not show any benefits for retinopathy of more intensive blood pressure lowering.

**2.1.5. Duration of diabetes**

Yau [41] conducted a review of 35 studies (1980–2008) researching the global prevalence and major risk factors of diabetic retinopathy and concluded that longer diabetes duration was a major risk factor in people with diabetes.

Scanlon [42] worked with colleagues in the UK looking at the risk of diabetic retinopathy at first screen in UK screening programs in children at 12 and 13 years of age and found that the greatest risk of retinopathy was in those with longer diabetes duration, in particular those who developed diabetes under the age of 2 years.

**2.1.6. Ethnicity**

Ethnicity variations in the incidence of diabetic retinopathy were first reported in 2003 in the Barbados Eye Study [43] where, in Type 1 diabetes, the risk of any DR was increased in the Asian minority and the risk of sight threatening DR was increased in the Africans compared to white Caucasians. In type 2 diabetes, the risk of sight threatening DR was increased for all non-Caucasians.

In 2007, Simmons reported [44] from New Zealand that that moderate or more severe retinopathy is more common in Polynesians than Europeans but concluded that the reasons for this are unclear but may be related to long-standing hyperglycemia.

In 2009, Raymond [45] reported that compared to the ethnic minority group of Southern Asians with Type 2 diabetes

had a higher prevalence of diabetic retinopathy. This was also associated with higher systolic and diastolic blood pressures, HbA1c and total cholesterol, and younger age when diagnosed with diabetes. Their life expectancy was also less.

In 2012, Sivaprasad [2] reported the results of a cross-sectional study (DRIVE UK) from West Yorkshire and South East London. Compared to 'White Europeans,' 'Blacks' and 'South Asians' had a higher prevalence of any DR, sight threatening DR and visual impairment. In type 2 diabetes, sight threatening DR was prevalent in 11.5% (95% CI 10.7 – 12.3%) of Afro-Caribbeans, 10.3% (95% CI 9.0–11.5%) of South Asians compared to 5.5% (95% CI 5.3% to 5.8%) of white Europeans.

In 2013, Thomas [46] reported that Asian Indians with Type 1 diabetes had a higher incidence of any DR and Africans with type 1 diabetes had a higher incidence of referable DR than Caucasians, whereas with Type 2 diabetes all non-Caucasians had a higher incidence of referable DR. It was difficult to separate ethnic risk factors from duration of diabetes and poor glycemic control.

### 2.1.7. Blood lipids

In 1996, Chew reported [47] from the ETDRS study that patients with elevated cholesterol levels at commencement of the study were twice as likely to have hard exudates in the retinal photographs.

In 2016, a report [48] of the association between lipids and diabetic retinopathy concluded that, in the studies that they had reviewed, there was a modest association between serum triglycerides or cholesterol and DR severity. A further report [49] concluded that stronger associations between specific lipoprotein species DR severity could be found.

### 2.1.8. Smoking

In type 1 diabetes Muhlhauser [50] and Karamanos [51] reported smoking to be a risk factor for progression. Muhlhauser commented that, 'while significant associations between smoking, and retinopathy and nephropathy respectively, were found, the relations were variable depending on the statistical model used.' However, more recently, in a Danish population [52] with Type 1 diabetes, neither a beneficial nor a harmful effect of smoking on long-term incidence of proliferative DR was found. Selective mortality among smokers and patients with PDR at baseline might provide at least part of the explanation for this.

In Type 2 diabetes, the evidence is controversial with the UKPDS reporting [53] that retinopathy is more likely to progress in nonsmokers which may also be partially explained by selective mortality among smokers.

### 2.1.9. Age

In Type 1 diabetes, the effect of age of onset of and the risk of progression of diabetic retinopathy is controversial. Hietala [54] reported from 1117 patients in the Finn Diane study that the highest risk of proliferative diabetic retinopathy is in age-at-onset group 5–14 years, whereas the lowest risk is in age-at-onset group 15–40 years. However, Scanlon [42] has reported data from screening programs in England, Scotland, Wales, and Northern Ireland on retinopathy levels for those

children having their first screen at the age of 12 years. In those diagnosed at the age of 2 years or less, 20% had retinopathy in one eye and 11% in two eyes. If a child was diagnosed over the age of 2 years, 8% had retinopathy in one eye and 2% in two eyes. The highest risk group for progression to referable retinopathy in their teenage years were those diagnosed at the age of 4 years or less.

The Wisconsin Epidemiological Study [8,9,55] reported that, in those aged <30 yrs taking insulin and who had diabetes of 10 years duration or less, the severity of retinopathy was related to older age at examination, whereas when the age at diagnosis was ≥30 yrs and taking insulin, the severity of retinopathy was related to younger age at diagnosis.

In Type 2 diabetes in the UKPDS [53], in those who already had retinopathy, progression was associated with older age.

### 2.1.10. Genetic predisposition

Kuo [56] wrote about the challenges in elucidating the genetics of diabetic retinopathy describing the greatest obstacles as a lack of power because of small sample size of available studies and a lack of phenotype standardization.

Hietala [57] found an increased risk of proliferative retinopathy in siblings with Type 1 diabetes, suggesting a genetic component. Other studies [58–64] have suggested a genetic component in the development of diabetic retinopathy in different populations.

### 2.1.11. Pregnancy

Pregnancy has, in its own right, been shown to be an independent risk factor for progression of DR in two studies [30,65]. Pregnancy has also been shown to be a risk factor for progression of DR when linked to other known risk factors such as baseline severity of retinopathy [31,32,66], poor metabolic control at conception [31], rapid improvement of glycemic control [30–32,66] (the early worsening phenomenon, poor metabolic control during pregnancy or the early postpartum period [30,65–67]), duration of diabetes [66,68,69], and chronic hypertension and pregnancy-induced hypertension [66].

### 2.1.12. Renal Function

There are some studies that report [70] that there are many patients with Type 2 diabetes and renal abnormalities (proteinuria and/or renal insufficiency) that show no signs of diabetic retinopathy or that, in Type 1 diabetes, many patients with normal renal function had retinopathy [71] in particular, the earlier stages of mild non-proliferative retinopathy. However, the majority of studies report a strong association between greater severity of retinopathy and decrease in renal function.

In 2001 Colhoun [72] reported from the WHO Multinational Study of Vascular Disease in Diabetes that, in both Type I and Type II diabetes, diabetic retinopathy, and proteinuria were strongly associated with renal failure.

In 2012, Grunwald [73] reported results from the Chronic Renal Insufficiency Cohort (CRIC) study, which was an observational, cross-sectional study of 2605 patients with chronic kidney disease. In this study, there was a strong association found between the severity of diabetic retinopathy and reduced glomerular filtration rate, which could not be



accounted for by other known risk factors. However, a further report from the same study [74] in 2019 concluded that progression of diabetic retinopathy was linked to progression of chronic renal insufficiency on univariable analysis but not on multivariable analysis. This suggested that similar risk factors may be causing progression of diabetic retinopathy and renal disease.

In 2013, He [75] reported a meta-analysis on diabetic retinopathy and renal disease. The pooled sensitivity from the 26 papers of diabetic retinopathy to predict diabetic nephropathy was 0.65 (95% CI 0.62, 0.68) with a specificity of 0.75 (95% CI 0.73, 0.78). However, when it came to the pooled sensitivity for proliferative DR to predict diabetic nephropathy, the pooled sensitivity from the 26 papers was only 0.25 (95% CI 0.16, 0.35) but the specificity was very high at 0.98 (95% CI 0.92, 1.00).

In 2013, Moriya [76] examined the interactive relationship between diabetic retinopathy (DR) and diabetic nephropathy (DN) patients in Japan with type 2 diabetes. The study reported that patients with microalbuminuria and DR showed the fastest estimated glomerular filtration rate decline and concluded that the combination of albuminuria and DR should be considered as risk factors of renal prognosis in type 2 diabetic patients.

In 2019, Kaewput [77] reported results from a multicentre nationwide cross-sectional study designed to assess the association between estimated glomerular filtration rate (GFR) and DR, severe DR, and severe visual impairment among 13,192 T2DM patients from 831 public hospitals in Thailand in the year 2013. Decreased GFR was independently associated with increased DR, severe DR, and severe visual impairment. The study concluded that the estimated GFR should be monitored in diabetic patients for DR awareness and prevention.

In 2019, Zhuang [78] reported results from a single-center retrospective observational study of 413 southern Chinese patients with type 2 diabetes mellitus conducted from December 2017 to November 2018. Stages of DR and DME were positively correlated with renal function, while stage of urine albumin-to-creatinine ratio performed a better relevance than stage of estimated glomerular filtration rate.

### **2.1.13. Combination of retinopathy and macroalbuminuria as a risk factor for cardiovascular events**

In 2007, Tong [79] reported that patients with the combination of diabetic retinopathy and macroalbuminuria had a higher incidence of cardiovascular and renal events and a higher mortality compared to those without these complications.

In 2012, Pugliese [80] reported a high prevalence of advanced DR in subjects with type 2 diabetes from the Renal Insufficiency and Cardiovascular Events (RIACE) in the Italian Multicentre Study cohort.

### **2.1.14. Retinal vascular geometry, diabetic retinopathy, and renal function**

In 2004, Wong reported [81] that a large diameter of retinal veins was associated with the development of proteinuria and renal insufficiency. In 2011, Benitez-Aguirre [82] reported that

retinal vascular geometry predicts incident retinopathy in young people with type 1 diabetes. In 2012, Benitez-Aguirre [83] reported that retinal vascular geometry independently predicted incident renal dysfunction in young people with type 1 diabetes. Retinal vascular geometry (including length-to-diameter ratio [LDR] and simple tortuosity [ST]) was quantified from baseline retinal photographs.

### **2.1.15. Non-attendance at screening and clinic appointments**

In 2005, Zoega [84] reported that patients who were registered blind on the Icelandic National Registry had a long history of nonattendance in the Diabetic Retinopathy Screening Programme in Iceland compared with those with better visual outcomes. In 2009, Gray [85] reported on a study that suggested that clinic nonattendance is likely to be a risk factor for sight threatening retinopathy. This was confirmed in 2013 when Forster [86] reported from a cohort study of 6,556 residents with diabetes in inner London that patients who do not attend diabetic eye screening are at increased risk of developing STDR. In those with mild non-proliferative DR at first screen who subsequently missed two screens, the adjusted relative odds of developing proliferative or moderate-to-severe non-proliferative retinopathy compared to those who attended for screening were 5.72 (95% CI 7.43, 22.83;  $p = 0.013$ ). It was also confirmed by Scanlon [87] in 2014 who reported that, of those screened within 6 months of diagnosis, 2.3% had referable retinopathy and, 3 years or more after diagnosis, 4.2% had referable retinopathy. In 2012, Sachdeva [88] reported results from a telephone survey of people with diabetes who had not attended for DR screening. The study reported that attendance was poorest in younger individuals with poor HbA1c values and high blood pressure readings (systolic and diastolic). Fifty percent of those at highest risk of DR did not attend. In 2016, Scanlon [89] reported that those in the 18–34 year age group are least likely to attend promptly for screening after registration with a higher risk of referable diabetic retinopathy being present at the time of first screen. In 2018, Kashim [90] reported a systematic review on patients' nonattendance for diabetic retinopathy screening in Diabetic Eye Screening programs.

The review 16 studies between 2003 and 2017 concluded that nonattendance as linked to socio-economic deprivations and to the development of sight threatening DR.

In 2021, Kelly [91] reported reasons for nonattendance in the Irish National DR Screening Programme which included age (OR: 1.23 per decade away from 70; 95% CI: [1.22–1.24]), type 2 diabetes (OR: 1.10; 95% CI: [1.06–1.14]) and socio-economic deprivation (OR: 1.12; 95% CI: [1.09–1.16]). Additionally, this study reported that adverse weather conditions (freezing or below-zero) were also associated with non-attendance with an odds ratio of 1.57 (95% CI .45–1.7 and  $p < 0.001$ ).

### **2.1.16. Sleep apnea**

In 2010, West [92] reported that, in men with Type 2 diabetes, there is a strong association between diabetic retinopathy and maculopathy severity and obstructive sleep apnea, independent of conventional retinopathy risk factors.

In 2013, Banerjee [93] reported that, in Type 2 diabetes, the apnea-hypopnea index (AHI) of  $\geq 15$  events/hour was not associated with DR but minimum oxygen saturations during sleep may be associated and, in 2015 Zhang [94] reported a similar association between Type 2 diabetes, obstructive sleep apnea, and low oxygen saturations, of which the lowest oxygen saturations were associated with PDR.

Storgaard [95] In 2014, reported an association between people with Type 2 diabetes and sleep apnea and, in 2015, Manin [96] reported an association between people with Type 1 diabetes and sleep apnea. Manin also reported that obstructive sleep apnea was associated with DR severity.

In 2017, a meta-analysis by Zhu [97] of available studies concluded that obstructive sleep apnea is related to increased risk of DR in both Type 1 and Type 2 diabetes mellitus.

In 2019, Feher [98] reported, using the Royal College of General Practitioners Research and Surveillance Center database, that obstructive sleep apnea was prevalent in people with both type 1 and Type 2 diabetes across the range of overweight categories and not simply in the highest obesity class.

### 2.1.17. Anemia

Although anemia can cause retinopathy in its own right, it can also increase the progression of diabetic retinopathy without renal disease. It can lead to the progression of diabetic retinopathy [99–101] with an increased severity of diabetic retinopathy [102] and progression of proliferative diabetic retinopathy after laser photocoagulation [103] probably caused by an increase in retinal ischemia.

## 3. How could one improve the screening of these risk factors for the benefit of reduced sight loss for our patients with diabetes?

In recent years, progression of diabetic retinopathy has slowed in countries with higher socioeconomic levels due to better glycemic, blood pressure, and control of lipids. There is a concentration on these known risk factors in clinics overseen by diabetes physicians and primary care physicians.

It is also important to be aware of situations in which progression of diabetic retinopathy is more likely. In these circumstances, regular monitoring of retinopathy levels should take place. For example:

- a) a patient whose glycemic control improves over a short period of time due to commencing insulin or the individual becoming more interested in improving their control;
- b) a patient whose renal function is declining and who has not attended for eye screening;
- c) a patient with sleep apnea.

There are some situations in which it is important to monitor the diabetic retinopathy more closely such as in pregnancy or in the first 6 months postpartum.

From the point of view of an eye screening program, an HTA report [104] gave the results of Cox proportional hazards model for time to referable diabetic retinopathy for pre-proliferative DR (R2), proliferative DR (R3), and maculopathy (M1) to be:

Mild NPDR in both eyes at screening visit 7.13 (95% CI: 5.84 to 8.70)

Mild NPDR in one eye at screening visit 2.56 (95% CI: 2.05 to 3.20)

HbA1c (per 10 mmol/mol increase) 1.28 (95% CI: 1.23 to 1.34)

Duration of diabetes (per 5 year increase) 1.20 (95% CI: 1.16 to 1.24)

Total serum cholesterol (per 1 mmol/L) 1.12 (95% CI: 1.05 to 1.19)

Serum creatinine (per 10  $\mu$ mol/L) 1.04 (95% CI: 1.01 to 1.07)

The population under study had well-controlled B/P but, in a population that is not well controlled, this will be an important additional risk factor.

The HTA study developed a risk score that was related to the level of DR found in the eye and associated risk factors:

Mild non-proliferative DR in both eyes =  $1.96 + Y$

Mild non-proliferative DR in one eye =  $0.94 + Y$

No DR =  $0 + Y$

$Y = (0.25 \times (\text{HbA1c}/10)) + (0.18 \times \text{duration of diabetes}/5) + (0.11 \times \text{total cholesterol}) + (0.04 \times \text{serum creatinine}/10)$

These risk scores led to five groups that had a risk of 10–60% of developing referable diabetic retinopathy within 5 years.

Other risk factors were not included because they either did not reach statistical significance in the population or were recorded in too few numbers (e.g. renal function) or occurred infrequently (e.g. sleep apnea). This does not mean that they are not important in an individual with these conditions.

The problem for all diabetic retinopathy screening programs is having access to additional data items as well as the retinopathy screening results. The previous eye screening results are by far and away the biggest hazard ratio and it is very difficult in England to join up all the other risk factor items such as HbA1c and have them in the eye screening database. Hence, the UK National Screening Committee has advised an extension of the screening interval to 2 years for those people with diabetes who have been found to have no retinopathy on their previous two screening episodes [105]. The English NHS Diabetic Eye Screening Programme has tried for many years to link up risk factor data to eye screening data, but this has proved very difficult due mainly to commercial factors and data protection issues. However, this has been achieved in Scotland showing that it is possible. When the IT infrastructure in the NHS improves to be able to link other risk factor data together in a high percentage of patients, other risk factor data may be included in the screening algorithm for extension of screening intervals.

Other algorithms [106–108] have been developed that do include the extra risk factor data that can be used when this is readily available, and they have been tested in populations in Ireland [109] and Holland [110].

In any screening program, it is important to focus on non-attenders as these are the people who are most at risk of progression of DR and loss of vision. The NHS Diabetic Eye Screening Programme in England has introduced a standard [111] that is a Key Performance Indicator that all of the regional programs are judged against which has brought a key

measurement for each program of proportion of eligible people with diabetes who have not attended for routine digital screening in the previous 3 years. This has inevitably meant that much more attention is being paid to try to get regular non-attenders to attend for screening, which will have long-term beneficial visual results for those that do attend.

It is also important to try and focus on ad-hoc methods of detection of retinopathy in general medical clinics if a regular non-attender does attend. Is there some method available to the diabetologist for examining the retina and do they have the expertise to do so?

#### 4. Conclusion

This article has highlighted the important risk factors for progression of diabetic retinopathy and discussed how these risk factors might be better utilized to prevent sight loss in different health-care settings linked to the management of diabetes. In order to reduce the risk of progression of DR, one needs to control risk factors that are modifiable for that individual, e.g. glycemic control, blood pressure, lipids, renal function, and anemia.

#### 5. Expert opinion

In modern medicine, many clinicians work in specialist areas that do not look at an individual as a whole. For example, there are primary care physicians, nurses in primary and secondary care, diabetologists, nephrologists, vascular surgeons, neurologists, gastroenterologists, podiatrists, and ophthalmologists looking after the care of these patients. Communication between primary and secondary care needs to be improved and there needs to be better communication between subspecialties. For example, it is tragic when a patient who is attending for renal dialysis three times a week suddenly loses vision and is found to have very advanced diabetic retinopathy and has not been attending for eye screening. Access to the data is not joined up. It should not be so difficult across the NHS to join up risk factor data to eye screening data for the benefit of patients, but it has been.

Data also need to improve in accuracy. For example, the date of diagnosis of Type 1 diabetes is often well remembered by the individual with diabetes but may be recorded in primary care as when the person joined that practice. Data protection is often used as a reason for making this linkage more difficult but, if this is in the patient's best interest, it should be made easier.

Research to improve uptake for screening in the vulnerable 18–45 year age groups will be important to reduce loss of vision in this working age group, who are historically poor attenders compared to people in the older age group with diabetes. I am hopeful that new cameras which do not require pupil dilation may encourage more of them to attend.

There may also be benefits in the automated reading of images so that a clinician who is not confident at any form of retinal examination can use a camera, which has some automated method of reading the images for patients who are regular non-attenders who present in an ad-hoc way. Automated reading may also help systematic eye screening

programs once they have been proven to have high enough sensitivities and specificities for the detection of any DR or sight threatening DR. In Scotland [112], they currently use an algorithm to detect any DR that has reduced the workload for their graders by taking images away from the grading queue that the automated method reads as no diabetic retinopathy.

What I would like to see in the next 10 years (and should be possible) is:

- (a) Use of new camera technology that does not require dilation of the pupil in 90% of people with diabetes. A small percentage will always need dilation, but I believe that this should be less than 10%.
- (b) Use of artificial intelligence software to take out images that show no retinopathy to a high level of specificity.
- (c) Linkage of data so that screening services, those looking after people with diabetes, and the individuals themselves have easy access to joined up data that includes screening grading results and relevant risk factor data.

#### Declaration of interest

P Scanlon has received speaker's fees from Topcon and Bayer PLC, and a department research grant from Bayer PLC.

The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

#### Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

#### Funding

The authors have no funding to report.

#### References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Kocur I, Resnikoff S. Visual impairment and blindness in Europe and their prevention. *Br J Ophthalmol*. 2002 Jul;86(7):716–722.
2. Sivaprasad S, Gupta B, Gulliford MC, et al. Ethnic variation in the prevalence of visual impairment in people attending diabetic retinopathy screening in the United Kingdom (DRIVE UK). *PLoS one*. 2012;7(6):e39608.
3. Liew G, Michaelides M, Bunce C. A comparison of the causes of blindness certifications in England and Wales in working age adults (16–64 years), 1999–2000 with 2009–2010. *BMJ Open*. 2014Feb12;4(2):e004015.
- This was the first report of reductions in blindness relating to the introduction of the NHS Diabetic Eye Screening Programme
4. Lawrenson JG, Bourmpaki E, Bunce C, et al. Trends in diabetic retinopathy screening attendance and associations with vision impairment attributable to diabetes in a large nationwide cohort. *Diabet Med*. 2021 Apr;38(4):e14425.
5. Scanlon PH. The contribution of the English NHS Diabetic Eye Screening Programme to reductions in diabetes-related blindness, comparisons within Europe, and future challenges. *Acta Diabetol*. 2021 Apr;58(4):521–530.



6. Open Athens. 2019. [Accessed 2022 January 10]. Available from: <https://www.openathens.net/>
7. Royal Society of Medicine. 2019. [Accessed 2022 January 10]. Available from: <https://www.rsm.ac.uk/the-library/>
8. Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol*. 1984 Apr;102(4):520–526.
- This was one of two early reports from the landmark The Wisconsin Epidemiologic Study of Diabetic Retinopathy.
9. Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol*. 1984 Apr;102(4):527–532.
- This was one of two early reports from the landmark The Wisconsin Epidemiologic Study of Diabetic Retinopathy.
10. Scanlon PH, Nevill CR, Stratton IM, et al. Prevalence and incidence of diabetic retinopathy (DR) in the UK population of Gloucestershire. *Acta Ophthalmol*. 2021 Jun 28;100(2):e560–e570.
11. Broe R, Rasmussen ML, Frydkjaer-Olsen U, et al. The 16-year incidence, progression and regression of diabetic retinopathy in a young population-based Danish cohort with type 1 diabetes mellitus: the Danish cohort of pediatric diabetes 1987 (DCPD1987). *Acta Diabetol*. 2014 Jun;51(3):413–420.
12. Wong TY, Mwamburi M, Klein R, et al. Rates of progression in diabetic retinopathy during different time periods: a systematic review and meta-analysis. *Diabetes Care*. 2009 Dec;32(12):2307–2313.
13. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. *Ophthalmology*. 1995 Jan;102(1):7–16.
14. Kiire CA, Horak K, Lee KE, et al. The period effect in the prevalence of proliferative diabetic retinopathy, gross proteinuria, and peripheral neuropathy in type 1 diabetes: a longitudinal cohort study. *PLoS one*. 2017;12(3):e0174979.
15. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology*. 1991 May;98(5 Suppl):786–806.
16. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology*. 1991 May;98(5 Suppl):823–833.
- This was the report that recorded the principal fundus photographic risk factors for progression of diabetic retinopathy.
17. Aldington SJ, Stratton IM, Matthews DR, et al. Relationship of retinal microaneurysm count to progression of retinopathy over 3 and 6 years in non-insulin dependent diabetes. *Diabetic Med*. 1995;12(Suppl 1):3.
18. Klein R, Meuer SM, Moss SE, et al. Retinal microaneurysm counts and 10-year progression of diabetic retinopathy. *Arch Ophthalmol*. 1995 Nov;113(11):1386–1391.
19. Sjolie AK, Klein R, Porta M, et al. Retinal microaneurysm count predicts progression and regression of diabetic retinopathy. Post-hoc results from the DIRECT Programme. *Diabet Med*. 2011 Mar;28(3):345–351.
20. Scanlon PH, Stratton IM, Histed M, et al. The influence of background diabetic retinopathy in the second eye on rates of progression of diabetic retinopathy between 2005 and 2010. *Acta Ophthalmol*. 2013 Aug;91(5):e335–9.
21. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993 Sep 30; 329(14):977–986.
- This work is a landmark clinical trial that confirmed that improved glycaemic control delayed the progression of diabetic retinopathy.
22. Diabetes Control and Complications Trial. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus. *J Pediatr*. 1994 Aug;125(2):177–188.
23. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998 Sep 12;352(9131):837–853.
24. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998 Sep 12;352(9131): 854–865.
25. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. *Ophthalmology*. 2009 Mar;116(3):497–503.
26. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. *Ophthalmology*. 2008 Nov;115(11):1859–1868.
27. Klein BE. Progression of retinopathy in persons with type 2 diabetes: new data, same conclusions? *Pol Arch Med Wewn*. 2010 Oct;120(10):413–416.
28. DCCT. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Arch Ophthalmol*. 1998 Jul;116(7):874–886.
29. Henricsson M, Berntorp K, Fernlund P, et al. Progression of retinopathy in insulin-treated type 2 diabetic patients. *Diabetes Care*. 2002 Feb;25(2):381–385.
30. The Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. *Diabetes Care*. 2000 Aug;23(8):1084–1091.
31. Chew EY, Mills JL, Metzger BE, et al. Metabolic control and progression of retinopathy. The Diabetes in Early Pregnancy Study. *Diabetes Care*. 1995 May;18(5):631–637. National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study
32. Phelps RL, Sakol P, Metzger BE, et al. Changes in diabetic retinopathy during pregnancy. Correlations with regulation of hyperglycemia. *Arch Ophthalmol*. 1986 Dec;104(12):1806–1810.
33. Kim YJ, Shin S, Han DJ, et al. Long-term effects of pancreas transplantation on diabetic retinopathy and incidence and predictive risk factors for early worsening. *Transplantation*. 2018 Jan;102(1):e30–e38.
34. Merlotti C, Ceriani V, Morabito A, et al. Bariatric surgery and diabetic retinopathy: a systematic review and meta-analysis of controlled clinical studies. *Obes Rev*. 2017 Mar;18(3):309–316.
35. Feldman-Billard S, Larger É, Massin P. Early worsening of diabetic retinopathy after rapid improvement of blood glucose control in patients with diabetes. *Diabetes Metab*. 2018 Feb;44(1):4–14.
36. Joner G, Brinchmann-Hansen O, Torres CG, et al. A nationwide cross-sectional study of retinopathy and microalbuminuria in young Norwegian type 1 (insulin-dependent) diabetic patients. *Diabetologia*. 1992 Nov;35(11):1049–1054.
37. Matthews DR, Stratton IM, Aldington SJ, et al. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. *Arch Ophthalmol*. 2004 Nov;122(11):1631–1640.
38. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Bmj*. 1998 Sep 12;317(7160): 703–713.
39. Chew EY, Ambrosius WT, Davis MD, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med*. 2010 Jul 15;363(3):233–244.
40. Patel A, Group AC, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007 Sep 8;370(9590):829–840.

41. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35(3):556–564.
42. Scanlon PH, Stratton IM, Bachmann MO, et al. Risk of diabetic retinopathy at first screen in children at 12 and 13 years of age. *Diabet Med*. 2016 Dec;33(12):1655–1658.
43. Leske MC, Wu SY, Hennis A, et al. Incidence of diabetic retinopathy in the Barbados Eye Studies. *Ophthalmology*. 2003 May;110(5):941–947.
44. Simmons D, Clover G, Hope C. Ethnic differences in diabetic retinopathy. *Diabet Med*. 2007 Oct;24(10):1093–1098.
45. Raymond NT, Varadhan L, Reynolds DR, et al. Higher prevalence of retinopathy in diabetic patients of south Asian ethnicity compared to white Europeans in the community: a cross sectional study. *Diabetes Care*. 2009 Dec 15;32(3):410–415.
46. Thomas RL, Distiller L, Luzio SD, et al. Ethnic differences in the prevalence of diabetic retinopathy in persons with diabetes when first presenting at a diabetes clinic in South Africa. *Diabetes Care*. 2013;36(2):336–341.
47. Chew EY, Klein ML, Ferris FL 3rd, et al. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22. *Arch Ophthalmol*. 1996 Sep;114(9):1079–1084.
48. Modjtahedi BS, Bose N, Papakostas TD, et al. Lipids and diabetic retinopathy. *Semin Ophthalmol*. 2016;31(1–2):10–18.
49. Lyons TJ, Jenkins AJ, Zheng D, et al. Diabetic retinopathy and serum lipoprotein subclasses in the DCCT/EDIC cohort. *Invest Ophthalmol Vis Sci*. 2004 Mar;45(3):910–918.
50. Muhlhauser I, Bender R, Bott U, et al. Cigarette smoking and progression of retinopathy and nephropathy in type 1 diabetes. *Diabet Med*. 1996 Jun;13(6):536–543.
51. Karamanos B, Porta M, Songini M, et al. Different risk factors of microangiopathy in patients with type I diabetes mellitus of short versus long duration. The EURODIAB IDDM Complications Study. *Diabetologia*. 2000 Mar;43(3):348–355.
52. Gaedt Thorlund M, Borg Madsen M, Green A, et al. Is smoking a risk factor for proliferative diabetic retinopathy in type 1 diabetes? *Ophthalmol J Int D'ophtalmologie Int J Ophthalmol Zeitschrift Fur Augenheilkunde*. 2013;230(1):50–54.
53. Stratton IM, Kohner EM, Aldington SJ, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. *Diabetologia*. 2001 Feb;44(2):156–163.
- **This work is a landmark clinical trial that confirmed that improved glycaemic and B/P control delayed the progression of diabetic retinopathy.**
54. Hietala K, Harjutsalo V, Forsblom C, et al. Age at onset and the risk of proliferative retinopathy in type 1 diabetes. *Diabetes Care*. 2010 Jun;33(6):1315–1319.
55. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of diabetic retinopathy. XIV. Ten-year incidence and progression of diabetic retinopathy. *Arch Ophthalmol*. 1994 Sep;112(9):1217–1228.
56. Kuo JZ, Wong TY, Rotter JI. Challenges in elucidating the genetics of diabetic retinopathy. *JAMA Ophthalmol*. 2014 Jan;132(1):96–107.
57. Hietala K, Forsblom C, Summanen P, et al. Heritability of proliferative diabetic retinopathy. *Diabetes*. 2008 Aug;57(8):2176–2180.
58. Jie X, Zhengxuan J, Liang Z, et al. Analysis of genetic susceptibility to proliferative diabetic retinopathy in Han patients with type 2 diabetes from Southern China by whole exome sequencing and SnpShot. *Chin J Exper Ophthalmol*. 2018;36(1): 31–40.
59. Leslie RD, Pyke DA. Diabetic retinopathy in identical twins. *Diabetes*. 1982 Jan;31(1):19–21.
60. Looker HC, Nelson RG, Chew E, et al. Genome-wide linkage analyses to identify Loci for diabetic retinopathy. *Diabetes*. 2007 Apr;56(4):1160–1166.
61. Rema M, Saravanan G, Deepa R, et al. Familial clustering of diabetic retinopathy in South Indian Type 2 diabetic patients. *Diabet Med*. 2002 Nov;19(11):910–916.
62. Zhang X, Gao Y, Zhou Z, et al. Familial clustering of diabetic retinopathy in Chongqing, China, type 2 diabetic patients. *Eur J Ophthalmol*. 2010;20(5):911–918.
63. Hallman DM, Huber JC Jr., Gonzalez VH, et al. Familial aggregation of severity of diabetic retinopathy in Mexican Americans from Starr County, Texas. *Diabetes Care*. 2005 May;28(5):1163–1168.
64. Arar NH, Freedman BI, Adler SG, et al. Heritability of the severity of diabetic retinopathy: the FIND-Eye study. *Invest Ophthalmol Vis Sci*. 2008 Sep;49(9):3839–3845.
65. Klein BE, Moss SE, Klein R. Effect of pregnancy on progression of diabetic retinopathy. *Diabetes Care*. 1990 Jan;13(1):34–40.
66. Rosenn B, Miodovnik M, Kranias G, et al. Progression of diabetic retinopathy in pregnancy: association with hypertension in pregnancy. *Am J Obstet Gynecol*. 1992 Apr;166(4):1214–1218.
67. Lauszus F, Klebe JG, Bek T. Diabetic retinopathy in pregnancy during tight metabolic control. *Acta Obstet Gynecol Scand*. 2000 May;79(5):367–370.
68. Dibble CM, Kochenour NK, Worley RJ, et al. Effect of pregnancy on diabetic retinopathy. *Obstet Gynecol*. 1982 Jun;59(6):699–704.
69. Temple RC, Aldridge VA, Sampson MJ, et al. Impact of pregnancy on the progression of diabetic retinopathy in Type 1 diabetes. *Diabet Med*. 2001 Jul;18(7):573–577.
70. Wolf S, Arend O, Toonen H. Measurement of retinal micro- and macrocirculation in patients with diabetes mellitus with scanning laser ophthalmoscopy. *Clin Vis Sci*. 1992;7:462–469.
71. Bulum T, Prkacin I, Duvnjak L. High prevalence of retinopathy in patients with type 2 diabetes and normal renal function. *Nephrol Dialysis Transplantation*. 2017;32(suppl\_3):iii278–iii278.
72. Colhoun H, Lee E, Bennett P, et al. Risk factors for renal failure: the WHO multinational study of vascular disease in diabetes. *Diabetologia*. 2001;Supplement 2:S46–53.
73. Grunwald JE, Alexander J, Ying G-S. Retinopathy and chronic kidney disease in the chronic renal insufficiency cohort (CRIC) study. *Arch Ophthalmol*. 2012;130(9):1136.
- **This work was at the forefront in showing the link between diabetic retinopathy and Chronic Renal Insufficiency**
74. Grunwald JE, Pistilli M, Ying GS, et al. Association between progression of retinopathy and concurrent progression of kidney disease: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. *JAMA Ophthalmol*. 2019 Jul 1;137(7):767–774.
- **This work was at the forefront in showing the link between diabetic retinopathy and Chronic Renal Insufficiency.**
75. He F, Xia X, Wu XF, et al. Diabetic retinopathy in predicting diabetic nephropathy in patients with type 2 diabetes and renal disease: a meta-analysis. *Diabetologia*. 2013;56(3):457–466.
76. Moriya T, Tanaka S, Kawasaki R, et al. Diabetic retinopathy and microalbuminuria can predict macroalbuminuria and renal function decline in Japanese type 2 diabetic patients: Japan Diabetes Complications Study. *Diabetes Care*. 2013 Sep;36(9):2803–2809.
77. Kaewput W, Thongprayoon C, Rangsin R, et al. Associations of renal function with diabetic retinopathy and visual impairment in type 2 diabetes: a multicenter nationwide cross-sectional study. *World J Nephrol*. 2019 Feb 21;8(2):33–43.
78. Zhuang X, Cao D, Yang D, et al. 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*. 2019;9(9):e031194–e031194.
79. Tong PC, Kong AP, So WY, et al. Interactive effect of retinopathy and macroalbuminuria on all-cause mortality, cardiovascular and renal end points in Chinese patients with Type 2 diabetes mellitus. *Diabet Med*. 2007 Jul;24(7):741–746.
80. Pugliese G, Solini A, Zoppini G, et al. High prevalence of advanced retinopathy in patients with type 2 diabetes from the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter Study. *Diabetes Res Clin Pract*. 2012;98(2):329–337.
81. Wong TY, Shankar A, Klein R, et al. Retinal vessel diameters and the incidence of gross proteinuria and renal insufficiency in people with type 1 diabetes. *Diabetes*. 2004 Jan;53(1):179–184.
82. Benitez-Aguirre P, Craig ME, Sasongko MB, et al. Retinal vascular geometry predicts incident retinopathy in young people with type

- 1 diabetes: a prospective cohort study from adolescence. *Diabetes Care*. 2011 Jul;34(7):1622–1627.
83. Benítez-Aguirre PZ, Sasongko MB, Craig ME, et al. Retinal vascular geometry predicts incident renal dysfunction in young people with type 1 diabetes. *Diabetes Care*. 2012;35(3):599–604.
  84. Zoega GM, Gunnarsdóttir T, Björnsdóttir S, et al. Screening compliance and visual outcome in diabetes. *Acta Ophthalmologica Scandinavica*. 2005 Dec;83(6):687–690.
  - **This work was important in showing the link between screening compliance and visual outcome.**
  85. Gray R, Blades C, Jobson C. Screening clinic non-attendance and the risk of sight threatening retinopathy. *Eur J Ophthalmol*. 2009;19(3):510.
  86. Forster AS, Forbes A, Dodhia H, et al. Non-attendance at diabetic eye screening and risk of sight-threatening diabetic retinopathy: a population-based cohort study. *Diabetologia*. 2013 Oct;56(10):2187–2193.
  87. Scanlon PH, Aldington SJ, Stratton IM. Delay in diabetic retinopathy screening increases the rate of detection of referable diabetic retinopathy. *Diabet Med*. 2014 Apr;31(4):439–442.
  88. Sachdeva A, Stratton IM, Unwin J, et al. Diabetic retinopathy screening: study to determine risk factors for non-attendance. *Diabetes Prim Care*. 2012;14(5): 308–316
  89. Scanlon PH, Stratton IM, Leese GP, et al. Screening attendance, age group and diabetic retinopathy level at first screen. *Diabet Med*. 2016 Jul;33(7):904–911.
  90. Kashim RM, Newton P, Ojo O. Diabetic retinopathy screening: a systematic review on patients' non-attendance. *Int J Environ Res Public Health*. 2018;15(1):157.
  91. Kelly SR, Loiseleur AR, Pandey R, et al. Factors associated with non-attendance in the Irish national diabetic retinopathy screening programme (INDEAR study report no. 2). *Acta Diabetol*. 2021 May;58(5):643–650.
  92. West SD, Groves DC, Lipinski HJ, et al. The prevalence of retinopathy in men with Type 2 diabetes and obstructive sleep apnoea. *Diabet Med*. 2010 Apr;27(4):423–430.
  - **This work was important in showing the link between Type 2 diabetes and obstructive sleep apnoea.**
  93. Banerjee D, Leong WB, Arora T, et al. The potential association between obstructive sleep apnea and diabetic retinopathy in severe obesity-the role of hypoxemia. *PLoS one*. 2013;8(11):e79521.
  94. Zhang R, Guo X, Guo L, et al. Prevalence and associated factors of obstructive sleep apnea in hospitalized patients with type 2 diabetes in Beijing, China 2. *J Diabetes*. 2015 Jan;7(1):16–23.
  95. Storgaard H, Mortensen B, Almdal T, et al. At least one in three people with Type 2 diabetes mellitus referred to a diabetes centre has symptomatic obstructive sleep apnoea. *Diabet Med*. 2014 Nov;31(11):1460–1467.
  96. Manin G, Pons A, Baltzinger P, et al. Obstructive sleep apnoea in people with Type 1 diabetes: prevalence and association with micro- and macrovascular complications. *Diabet Med*. 2015 Jan;32(1):90–96.
  97. Zhu Z, Zhang F, Liu Y, et al. Relationship of obstructive sleep apnoea with diabetic retinopathy: a meta-analysis. *Biomed Res Int*. 2017;2017:5.
  98. Feher M, Hinton W, Munro N, et al. Obstructive sleep apnoea in Type 2 diabetes mellitus: increased risk for overweight as well as obese people included in a national primary care database analysis. *Diabet Med*. 2019 Oct;36(10):1304–1311.
  99. Ranil P, Raman R, Rachepalli S, et al. Anemia and diabetic retinopathy in type 2 diabetes mellitus. *J Assoc Physicians India*. 2010;58:91–98.
  100. Chung JO, Park SY, Chung DJ, et al. Relationship between anemia, serum bilirubin concentrations, and diabetic retinopathy in individuals with type 2 diabetes. *Medicine (Baltimore)*. 2019;98(43):e17693. In eng.
  101. Li Y, Yu Y, VanderBeek BL. Anaemia and the risk of progression from non-proliferative diabetic retinopathy to vision threatening diabetic retinopathy. *Eye (Lond)*. 2020;34(5):934–941.
  102. Traveset A, Rubinat E, Ortega E, et al. Lower hemoglobin concentration is associated with retinal ischemia and the severity of diabetic retinopathy in type 2 diabetes. *J Diabetes Res*. 2016;2016:3674946.
  103. Sepulveda FJ, Perez P, Medinilla MG, et al. Anemia as a factor related to the progression of proliferative diabetic retinopathy after photocoagulation. *J Diabetes Complications*. 2012;26(5):454–457.
  104. Scanlon PH, Aldington SJ, Leal J, et al. Development of a cost-effectiveness model for optimisation of the screening interval in diabetic retinopathy screening. *Health Technol Assess*. 2015 Sep;19(74):1–116.
  105. NSC. UK NSC screening recommendation on changing the screening interval from every year to every 2 years for people at low risk of sight loss 2016. [Accessed 2022 January 10]. Available from: <https://view-health-screening-recommendations.service.gov.uk/diabetic-retinopathy/>
  106. Stratton IM, Aldington SJ, Taylor DJ, et al. A simple risk stratification for time to development of sight-threatening diabetic retinopathy. *Diabetes Care*. 2013 Mar;36(3):580–585.
  - **This was the first report of the method of risk stratification based on two negative screens.**
  107. Aspelund T, Thórnisdóttir O, Ólafsdóttir E, et al. Individual risk assessment and information technology to optimise screening frequency for diabetic retinopathy. *Diabetologia*. 2011 Oct;54(10):2525–2532.
  108. Lund SH, Aspelund T, Kirby P, et al. Individualised risk assessment for diabetic retinopathy and optimisation of screening intervals: a scientific approach to reducing healthcare costs. *Br J Ophthalmol*. 2016 May;100(5):683–687.
  109. Smith JJ, Wright DM, Stratton IM, et al. Testing the performance of risk prediction models to determine progression to referable diabetic retinopathy in an Irish type 2 diabetes cohort. *Br J Ophthalmol*. 2021 Apr 26. DOI:10.1136/bjophthalmol-2020-318570.
  110. van der Heijden AA, Nijpels G, Badloe F, et al. Prediction models for development of retinopathy in people with type 2 diabetes: systematic review and external validation in a Dutch primary care setting. *Diabetologia*. 2020 Jun;63(6):1110–1119.
  111. PHE. Diabetic eye screening standards valid for data collected from 1 April 2019 2019. [Accessed 2022 January 10]. Available from: <https://www.gov.uk/government/publications/diabetic-eye-screening-programme-standards/diabetic-eye-screening-standards-valid-for-data-collected-from-1-april-2019>
  112. Philip SL, Black N, Sharp M, et al. Impact of introducing automated grading into the Scottish national diabetic retinopathy screening programme. *Manchester: Diabetic Medicine*; 2017. p. 457.