Risk factors associated with progression to referable retinopathy: a type 2 diabetes mellitus cohort study in the Republic of Ireland

Smith, J. J., Wright, D. M., Scanlon, P., & Lois, N. (2020). Risk factors associated with progression to referable retinopathy: a type 2 diabetes mellitus cohort study in the Republic of Ireland. *Diabetic Medicine*, *37*(6), 1000-1007. https://doi.org/10.1111/dme.14278

Published in:
Diabetic Medicine

Document Version:
Publisher's PDF, also known as Version of record

DIABETIC Medicine

DIABETES UK
KNOW DIABETES. FIGHT DIABETES.

Risk factors associated with progression to referable retinopathy: A Type 2 Diabetes Mellitus cohort study in Ireland

Journal:	*Diabetic Medicine*
Manuscript ID	DME-2019-00713.R2
Manuscript Type:	Research Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Smith, John; Queen's University Belfast, Wellcome-Wolfson Institute for Experimental Medicine Wright, David; Queen's University Belfast, Centre for Public Health Scanlon, Peter; Gloucestershire Hospitals NHS Foundation Trust, Ophthalmology Lois, Noemi; Queens University Belfast School of Medicine, Dentistry and Biomedical Sciences, Wellcome-Wolfson Institute for Experimental Medicine
Keywords:	microvascular disease, retinopathy, screening

Associate Editor
Decision Letter to Author:
The authors have responded comprehensively to the concerns of the peer reviewers and Editorial team.

We would like to thank the Editorial Board and the Reviewers for all their input in our manuscript.

Reviewer comments:

Reviewer: 1

Comments to the Author
I appreciate the careful responses of the authors on my statistical issues. I still do not agree on some points with the authors, but it would be unfair to "block" the paper any further, as many papers in clinical journals give considerably LESS attention to statistical analyses. However, allow me to come back to one point (on which I do not expect the authors to react, but maybe they might consider it for future work). They write: "The Cox model was chosen largely because it is more familiar to a clinical audience. We acknowledge that for prognostic purposes a fully parametric model would be preferable but the aim here was simply to identify risk factors, hence our choice." The authors are wrong here, because parametric regressions models can of course do BOTH, give prognoses as well as standard estimates for risk factors, as such, this is no argument for preferring the Cox model. On the contrary, parametric regression models in general give BETTER (in the sense of better to interpret) risk estimates than the Cox model. The Cox model gives hazard ratios, which are only consumable when incorrectly interpreted as risks (e.g., Sutradhar/Austin, 2018). So it is maybe a bit provocative, but also close to the truth to say that the Cox model neither allows prognoses in the time course, nor sensible risk estimates ...
Sutradhar R, Austin PC. Relative rates not relative risks: addressing a widespread misinterpretation of hazard ratios. Ann Epidemiol. 2018 Jan;28(1):54-57.

We would like thank Reviewer 1 for accepting our approach. We do understand the comment made by the Reviewer and her/his recommendation that in future work, a fully parametric approach might be better for both risk estimation and prognosis.

Reviewer: 2

Comments to the Author
This manuscript reports the results from a cohort study investigating the risks of progression to referable diabetic retinopathy in people with type 2 diabetes in Ireland. The manuscript has been re-submitted after a previous review and the authors have addressed the reviewer's comments. I have only a few formatting requests.

In the abstract and results please state the level of confidence for all reported confidence intervals

We have now clearly labelled the confidence intervals in the abstract and results section of the manuscript.

On page 17 the font size is different for two sections of text, is this intentional?

We are very sorry as we cannot find the section in the text where the font size is different. We have now made sure all the text is in Times New Roman font 12.

Page 20; please insert a space in "64mmol/mol"

Thank you very much for this correction; space now inserted.

Reviewer: 3
Comments to the Author
There may be an underlying assumption in the non-specialist community that DR is by definition always progressive; a comment regarding this might be valuable in the Discussion since it impinges on the need or not for frequent screening.

We thank Reviewer 3 for this comment.

In order to address this issue we have added to the manuscript (Discussion section): " It should be noted, though, that although most people with diabetes, if not all, will develop DR at one point in their lives, progression from mild NPDR to more severe stages may not always occur. Furthermore, in only a small proportion of patients with DR, DMO or PDR will ensue."

The source of the patient cohort may not be entirely clear to non-UK readers. I wonder if instead of "Ireland" the use of "The Republic of Ireland" might clearly differentiate.

We agree with Reviewer 3.

In order to address this issue we have refer to the Republic of Ireland, when pertinent, throughout the manuscript, including it's title.

Risk factors associated with progression to referable retinopathy:

A Type 2 Diabetes Mellitus cohort study in the Republic of Ireland

John J Smith, MRCOphth, FRCSI[1]

David M Wright, PhD[2]

Peter Scanlon, MD, FRCP, DCH, DRCOG, DO, FRCOphth, FHEA[3]

Noemi Lois, MD, PhD, FRCS(Ed), FRCOphth[1]

From the Wellcome-Wolfson Institute for Experimental Medicine[1] and the Centre for Public Health, [2] Queens University, Belfast, and Gloucestershire Hospitals NHS Foundation Trust, Gloucester,[3] United Kingdom.

Corresponding Author: Professor Noemi Lois, MD, PhD, FRCS(Ed), FRCOphth; Wellcome-Wolfson Institute for Experimental Medicine, School of Medicine, Dentistry & Biomedical Sciences, Queen's University Belfast, 97 Lisburn Road, BT9 7JL Belfast, United Kingdom. Telephone: 028 9097 2222; Email: n.lois@qub.ac.uk.

Presented partially at the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), Vancouver, Canada, April 28th – May 2nd, 2019.

Conflict of interest: For all authors = None

Novelty statement

- In an Irish cohort of people with type 2 diabetes, mild retinopathy, when compared with no retinopathy, at screening was strongly associated with increased risk of progression to referable retinopathy.
- Increased HbA1c, systolic blood pressure and triglycerides were associated with increased risk of referral.
- Increased diastolic blood pressure was associated with reduced risk of referral.
- This is the first comprehensive study evaluating risk factors and rates of referral in an Irish population with type 2 diabetes; knowledge of risk factors and strength of their association with incidence/progression of retinopathy is essential if individualised risk-based screening programmes are to be implemented.

Abstract

Objective: To determine factors associated with progression to referable diabetic retinopathy in people with type 2 diabetes in Ireland.

Research Design and Methods: Dynamic cohort of 2,770 people with type 2 diabetes recruited between April 2005 and July 2013. Systemic factors [systolic and diastolic blood pressure (BP); glycosylated haemoglobin (HbA1c); lipid levels; body mass index (BMI)] and baseline diabetic retinopathy grading results were evaluated at four-monthly and yearly intervals, respectively. Associations between risk factors (most recently recorded value, and rate of change in value between pairs of consecutive systemic evaluations) and development of referable diabetic retinopathy were estimated using Cox proportional hazards models.

Results: There was a four-fold increased risk of progression to referral when there was retinopathy, when compared with no retinopathy, at the baseline (hazard ratio [HR] 4.02; 95% confidence interval [CI] 2.80, 5.78; p<0.001). Higher current values of HbA1c (HR 1.22; 95% CI 1.11, 1.34; p<0.001), systolic BP (HR 1.29; 95% CI 1.15, 1.45; p<0.001) and triglyceride levels (HR 1.10; 95% CI 1.03, 1.18; p=0.004) were associated with increased risk of referral. Higher current BMI (HR 0.83; 95% CI 0.73, 0.95; p=0.007) and diastolic BP (HR 0.91; 95% CI 0.85, 0.97; p=0.006) were associated with reduced risk of referral.

Conclusions: Presence of retinopathy at baseline was strongly associated with increased risk of referral. Modest associations between systemic factors and risk of progression to referable retinopathy were detected.

Introduction

Screening for diabetic retinopathy (DR) is essential to prevent sight loss in people with diabetes. It fulfils all criteria set by Wilson and Jungner [1)], later adopted by the World Health Organisation [2] (WHO), to justify screening for a disease. Screening for DR and timely treatment of its complications, diabetic macular oedema (DMO) and proliferative diabetic retinopathy (PDR), prevents over 70% of expected cases of blindness [3]. In Iceland, following the introduction of screening, the prevalence of legal blindness as a result of diabetes decreased from 2.4% to 0.5%, demonstrating its substantial benefit [4].

Digital retinal imaging and grading by experienced graders is the standard method used in DR screening programmes in Europe [5]. The need for fixed annual ophthalmic evaluations for all people with type 2 diabetes is being revised as it is no longer widely supported in an era where the prevalence of diabetes has reached epidemic proportions, there is increased life expectancy and improved diabetic control. The American Diabetes Association (ADA) advised extending the interval between screening episodes for people with well-controlled diabetes type 2 and no DR at the most recent evaluation [6]. In 2015 a health technology assessment concluded that if a risk model is employed with personalised intervals, low-risk groups could be safely and effectively screened every 5 years [7]. A systematic review published in 2016 found little difference in clinical outcomes between screening annually or at 2-year intervals in low-risk people with diabetes type 2 [8].

The risk of a person with T2D progressing to referable DR and potentially vision-threatening DR (i.e. DMO and/or PDR) between two consecutive ophthalmic evaluations, which would indeed determine the appropriate screening interval, appears dependent on multiple risk factors, local and systemic. Establishing them in different populations is essential if personalised screening intervals are to be introduced.

The current study provides insight into risk factors for development of referable DR in the Irish population, from where very sparse data has been available to date.

Participants and Methods

1. Participant's cohort

A primary care-based screening programme, the Diabetes Watch Programme, developed by the public health service in the Republic of Ireland, offered care to people with diabetes type 2 ≥ 18 years of age registered with 20 General Practitioners' (GP) practices. Diagnosis and assessments adhered to established methods [9]. People with Type 1 diabetes and pre-diabetes and those currently accessing secondary care for diabetes type 2-related complications (other than ophthalmic) were excluded.

From February 2005 until December 2007, 1,265 individuals with pre-existing diabetes type 2 were recruited to the Diabetes Watch Programme. Subsequently, between February 2008 and July 2013 targeted screening of asymptomatic individuals identified 1,505 people with newly diagnosed diabetes type 2 in the same GP practices. All 2,770 people were enrolled in the Diabetes Watch Programme.

2. Systemic and ophthalmic evaluations.

Systemic evaluations were undertaken at four-month intervals by specialist nurses. Visits were combined with structured education. Systolic and diastolic blood pressure (BP), glycosylated haemoglobin (HbA1c), serum lipids and body mass index (BMI) were measured at each visit.

Participants recruited were offered voluntary enrolment into linked DR surveillance. Digital retinal imaging combined with masked image grading, as per the national screening programme for DR in England and Wales [10], commenced in the Diabetes Watch

Programme in 2006. Systemic and ophthalmic evaluations were linked; invitation to attend ophthalmic evaluations was dependent upon continued attendance at systemic evaluations in primary care. Retinal imaging was undertaken by trained technicians at or near the GP practice by fixed or mobile screening services on an annual basis. For each eye, best-corrected LogMAR visual acuity, with the best current refraction or pinhole, and dilated digital retinal imaging (two 45-degree colour photographs; one macula and one disc centred) were obtained. A single Topcon NW6S imaging system linked to a Nikon D80 succeeded by a D90 digital camera was used on the programme. Images were saved using a bespoke image capture system and then transferred to cloud-based image storage as part of the back-up process.

Individuals with clinically relevant disorders were referred to the hospital for management. Those deemed unsuitable for photographic assessment (e.g. inoperable media opacity) or previously identified visual threatening DR, were assigned an ophthalmologic examination using slit-lamp biomicroscopy.

3. Image grading

In accordance with the recommendations of the English National Screening Programme for Diabetic Retinopathy (ENSPDR) [10], image grading was a 3-stage process with graders at primary, secondary and tertiary/arbitration levels depending on experience and training. Bespoke software was used to manage and distribute images to specific graders. Grading staff underwent annual appraisal to ensure consistently high accuracy in grading; the online assessment tool of the ENSPDR was used to benchmark graders [11].

Graders recorded the gradable status of images and graded them as R1 (background: at least one microaneurysm and/or retinal haemorrhage); R2 (pre-proliferative: multiple haemorrhages and/or definite intra-retinal microvascular abnormality [IRMA] and/or venous

beading and/or venous reduplication); R3 (PDR) and M1 (two of the following: an exudate within 1-disc diameter of the centre of the fovea; a group of exudates within the macula; a microaneurysm or haemorrhage within 1-disc diameter of the centre of the fovea; provided this was associated with best-corrected visual acuity of >0.3 LogMAR [<6/12 Snellen equivalent]) or R0 or M0 (no retinopathy, no DMO, respectively). For this cohort study, a participant's retinopathy grading result and the need for referral (i.e. diagnosis of referable DR) was defined according to the consensus grading of their worst affected eye (e.g. if R0 M0 in the right eye and R1 M0 in the left eye, the patient's grading at study entry would have been R1 M0). Patients graded as R1M1, R2M0, R2M1, R3M0 or R3M1 in one/both eyes during the follow-up were considered to have referable DR. R0 referred to the absence of "overt" retinopathy, meaning there was no retinopathy detected based on fundus examination but without the use of other imaging technologies (e.g. fluorescein angiography, optical coherence tomography angiography).

4. Ethical Approval

Ethical approval for use of anonymised data was obtained from the Local Research Ethics Committee of the Republic of Ireland's Health Service Executive on 19th November 2015 (REC/15/041). Participants provided written informed consent to participate in the programme and for data collected to be used for research. This study adhered to principles detailed in the Declaration of Helsinki.

5. Statistical analysis

A Cox proportional hazards model was used to estimate associations between systemic and ocular factors and risk of developing referable DR. The structure of the Diabetes Watch Programme, with 4-monthly systemic evaluations and annual ophthalmic

surveillance, permitted evaluation of the influence of changes in systemic parameters over time (e.g. decreases in HbA1c as patients brought diabetes under control). Systemic measurements were included as time-varying covariates, dividing the observation period into segments, one for each pair of consecutive systemic evaluations. For each covariate a weighted average across time segments provided an estimate of the overall association with referable DR risk (i.e. a Hazard Ratio, HR). The overall estimates may be interpreted to represent associations found over relatively short time periods (months rather than years). Systemic measurements were represented in the model in two forms a) the most recently recorded value and b) the rate of change in the value between the two most recent evaluations. For each of the systemic measurements, rate of change was calculated by subtracting the value at the start of each time segment from the final value and dividing by segment length. The influences of both current values and rates of change were evaluated, being entered into the regression model as time-varying covariates. To reduce the risk of confounding between current values and rates of change for systemic measurements, rates were retained in the model only if they had low variance inflation factors on inclusion (i.e. little evidence of collinearity). The retinal grading outcome at the initial ophthalmic evaluation was included as an additional (time-independent) covariate. The model was stratified by gender. Observation of some individuals began at the time of diagnosis but for others it was delayed (i.e. they entered the programme with pre-existing diabetes). To account for this variation, duration of time since diagnosis of diabetes was used as a common time-scale and thus modelled implicitly (12)

All quantitative measurements were standardised prior to modelling by subtracting the median and dividing by the difference between the 75th percentile and the median. This approach was found to be less sensitive to outlying values for the rate variables (measurement

error is compounded when calculating rates) meaning that estimated HRs better represented ranges with most data support for each variable.

For an individual to be included in the model there had to be two complete systemic evaluations prior to at least one ophthalmic evaluation, to ensure that rates of change of the systemic covariates between consecutive assessments could be calculated. Participants with referable DR at baseline and those that had previously received treatment (i.e. only treatment-naïve patients were retained) were excluded. Participants lacking relevant information (e.g. date of birth, gender, date of diagnosis) were also excluded.

Variables investigated for their association with progression to referable DR in the model were: 1) most recently recorded values of systemic parameters; 2) rates of change between consecutive measurements in systemic parameters; and 3) retinopathy grading at initial assessment.

Results

There were 2,770 people with type 2 diabetes included. During the eight-year period of the programme, 9,604 ophthalmic evaluations occurred which were linked to 22,701 systemic evaluations, of which 19,172 (84%) had complete data for all variables selected. Of these, 1,770 people were eligible to be included in the Cox proportional hazards model (Figure 1) aimed at estimating risk of developing referable DR. A total of 9,576 systemic evaluations were conducted on the modelled cohort during follow-up and included in the survival analysis. One-hundred and forty-three individuals (8%) developed referable DR during the follow-up. Characteristics of the entire Diabetes Watch Programme cohort and of participants included in the model are shown in Table 1.

The outcome of the initial ophthalmic evaluation was strongly associated with risk of progression to referable DR. Participants with R1 were much more likely to be referred subsequently (54/259) than those with no retinopathy (76/1378). People with R1 were four times more likely to progress to referable DR than those with no retinopathy, after adjusting for all other variables (HR 4.02, 95% CI [2.80, 5.78]; p < 0.001; Table 2).

Higher values of the most recently recorded glycosylated haemoglobin (HbA1c) (HR 1.22, 95% CI [1.11, 1.34]; p=0.001), systolic blood pressure (HR 1.29, 95% CI [1.15, 1.45] p=0.001) and triglycerides (HR 1.10, 95% CI [1.03, 1.18]; p= 0.004) were all associated with increased risk of developing referable DR (Table 2). Interestingly, those with rapidly increasing triglyceride levels were slightly less likely to be referred than those with high but stable triglyceride levels (HR 0.94, 95% CI [0.90, 0.98] p=0.004) (Table 2). High current BMI (HR 0.83, 95% CI [0.78, 0.95]; p=0.007) and diastolic BP (HR 0.91, 95% CI [0.85, 0.97]; p=0.006) were associated with reduced referral risk (Table 2). Distributions of systemic variables included in the model are shown in Table 3.

Discussion

High HbA1c, systolic BP and triglycerides were all associated with increased risk of developing referable DR, whereas high BMI and diastolic BP were associated with reduced risk in this Irish population. The presence of any DR when entering the cohort, when compared with no "overt" retinopathy, markedly increased the risk of referral, with a four-fold increased risk in people with R1, M0 when compared with those with R0, M0.

The stage of DR appears to be a major determinant of risk of DR progression. In the UK Prospective Diabetes Study (UKPDS), a randomised clinical trial that examined the

effect of tight glycaemic control in people with diabetes type 2, 0.2% and 2.6% of people with no retinopathy at baseline (R0/ETDRS10) required laser at 3 and 9 years, respectively, when compared with 15% and 32% for those with mild to moderate non-proliferative DR (NPDR) (R2/ETDRS35-43) [13]. Stratton et al [14] estimated the risk of progression to sight threatening DR (defined as R2, R3 or M1 in either eye) in an individual with no retinopathy in either eye at presentation but who progressed to R1 in both eyes one year later to be approximately six times greater than that of someone with no DR in either eye on both occasions. If there was bilateral R1 at baseline and also one year later the risk of subsequent sight threatening DR was approximately18 times higher than if there was no retinopathy in either eye at both assessments. In agreement with these findings, in the Republic of Ireland's Irish population of the Diabetes Watch Programme, early signs of DR in people with diabetes type 2 were associated with markedly increased risk of referral when compared with no DR.

Several systemic risk factors were associated with progression to referable DR. One of these, HbA1c, is a well-recognised risk factor for development and progression of DR in people with type 2 diabetes [15-17]. In the UKPDS [16] for every percentage HbA1c point reduction (e.g. from 8% to 7%; 64 mmol/mol to 53 mmol/mol) there was a 37% reduction in risk of microvascular complications. Despite the relatively good diabetic control in our cohort (mean HbA1c 6.8%; 51 mmol/mol), the deleterious effect of HbA1c on risk of progression to referable DR was still observed underlining the importance of this risk factor on development/progression of DR.

The effect of BP in development and progression of DR is less clear. In the UKPDS intensive treatment reduced the incidence of DR [18]. But no consistent association was observed in the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) [19] in which high systolic BP was a significant risk factor for development of DR only in people

with younger-onset diabetes (onset <30 years of age) but not in those in whom diabetes developed later in life (onset at or after 30 years of age). In the Action to Control Cardiovascular Risks in Diabetes (ACCORD) Eye Study [20] lowering systolic BP did not significantly affect DR progression. A systematic review and meta-analysis revealed that intensive control of BP had preventive effects on 4-5 years incidence of DR but not on progression when DR was already present [21]. In the DWP, higher systolic blood pressure was associated with increased risk of progression to referable DR. It is possible that differences observed among studies on the effect of BP on incidence/progression of DR may relate to different baseline levels of BP in different populations (e.g. in intervention studies, if the levels of blood pressure at study entry were only mildly elevated, reducing the BP further may have not had an impact on reducing risk of retinopathy). It is also possible that certain risk factors may affect different populations in a different manner (i.e. some may be more susceptible than others). Of interest, in the Diabetes Watch Programme cohort, higher diastolic BP appeared protective. It could be speculated that the increased diastolic BP in people with high systolic BP would reduce pulse pressure [22] which, in turn, would have a positive effect reducing shear forces in retinal blood vessel walls, reducing blood vessel damage and progression of DR.

In the Diabetes Watch Programme cohort, elevated triglycerides were associated with increased risk of referral. A recently conducted meta-analysis of case-control studies in people with T1D and T2D found mean levels of serum triglycerides to be significantly higher in patients with DMO when compared with those without it [23]. It is not possible to determine whether the increased risk of referral associated with increased triglycerides observed in the Diabetes Watch Programme cohort was related to DMO, as referable DR included R2 and R3 (PDR) in addition to DMO. The increased risk associated with

triglycerides was higher in individuals with longer standing high levels when compared with those with rapid increases suggesting that time is required for the deleterious effects of triglycerides to occur. Other studies support a potential deleterious effect of dyslipidemia on the incidence of DR, DMO and PDR [24].

The protective effect of BMI on the development of referable DR, observed in the Diabetes Watch Programme cohort, appears counterintuitive. However, a recent systematic review and meta-analysis did not find higher BMI to be associated with increased risk of DR [25]. Furthermore, like in the Irish cohort presented here, other studies have found higher BMI to be protective [26, 27]. BMI provides an indication of general obesity whereas waist to hip ratio assesses abdominal obesity and visceral fat; the correlation between BMI and waist to hip ration varies considerably among individuals. Thus, BMI alone may not be adequate as a risk predictor [28]. Further studies are needed to better understand the effect of general and/or abdominal obesity on incidence and progression of DR in different populations.

The value of adding systemic risk factors to retinopathy grading, as determined in one or both eyes at one or two consecutive screening visits [14], with the goal of increasing the accuracy of estimates of risk of progression to advanced disease, whether referable retinopathy (R2, R3, M1) or sight threatening DR (R3, M1), remains to be fully elucidated. If predicted risk were more accurately determined by inclusion of systemic risk factors in addition to updated retinopathy grading, then combining clinical and screening platform data would be advisable, potentially leading to a more cost-effective screening. In this regard, an algorithm first developed in Iceland and validated in other populations, is available to determine individual risk and corresponding screening interval [29]. This algorithm uses retinopathy grade, gender, duration and type of diabetes but only HbA1c and systolic BP as

systemic risk factors. It is not known whether the accuracy of its predictions could be augmented by adding other risk factors that may be important in particular populations where the algorithm is going to be applied (e.g. triglycerides and diastolic BP in the Irish population, following findings of the Diabetes Watch programme presented herein).

Future studies evaluating risk factors should examine them differentially for DMO and PDR (rather than together, under umbrella terms of "referable DR" or "sight-threatening DR), given that consequences of DMO and PDR are different. DMO does not cause rapid visual loss or affect peripheral vision, unlike PDR which, if accompanied by contraction of the posterior hyaloid face and pre-retinal fibrosis, can rapidly progress to tractional retinal detachment (TRD) and loss of central and peripheral vision. It should be noted, though, that although most people with diabetes, if not all, will develop DR at one point in their lives, progression from mild NPDR to more severe stages may not always occur. Furthermore, in only a small proportion of patients with DR, DMO or PDR will ensue.

This study has several limitations. The requirements for the undertaking of the statistical analysis, as stated in the Methods section (above), meant that only data from 1775 of the 2770 participants could be used for the analysis. The structure of the statistical model with time-varying covariates precluded full adjustment for the interval censoring inherent in the data, reducing statistical power to detect associations, especially between rates of covariate change and referable DR. Furthermore, although the cohort of people with diabetes type 2 in the Diabetes Watch Programme constituted almost 20% of the total population with type 2 diabetes in the four county region of the Republic of Ireland, it is not possible to guarantee this group is representative of the Irish population with type 2 diabetes. It is also not known whether the sample will be representative either of people with undiagnosed diabetes or of those not attending screening programmes. However, baseline characteristics

of participants were very similar to those presented for a population of people with type 2 diabetes in community-based care elsewhere in Ireland [30] suggesting cohort participants may represent well the wider diabetic population. Another limitation of the study was the fact that participants were graded, at baseline and during the follow-up, based on the grading of the more severely affected eye (i.e. it is possible that the more severely affected eye at baseline was not the eye that develop referable DR during the follow-up). Furthermore, the categorisation of referable DR, as used in this study, hindered our ability to look separately for risk factors for DMO or PDR and may have disguised associations to one or the other which may have been revealed if these entities had been studied separately. Strengths include the standardised evaluation of participants, the relatively large cohort followed for a relatively long period of follow-up, the availability of systemic data at regular intervals in addition to the DR grading, and the use of not only single values of systemic risk factors but also their change over time in the statistical model.

Acknowledgement

The authors are very grateful to the administrative staff at HSE Primary Care, Navan, Co. Meath and Foresight Eye Care, Dundalk, Co. Louth, Ireland. The Authors would like to thank Ms B. Tiernan, the practitioner nurses from the 20 practices taking part in the DWP, the Diabetes Watch liaison nurse Celine Croarkin and Mr S. Ventakataswamy, Ocuco Ltd, Ireland. The Authors are very grateful to the Foresight Eye Care screening and grading staff, who undertook the image acquisition, grading and referral.

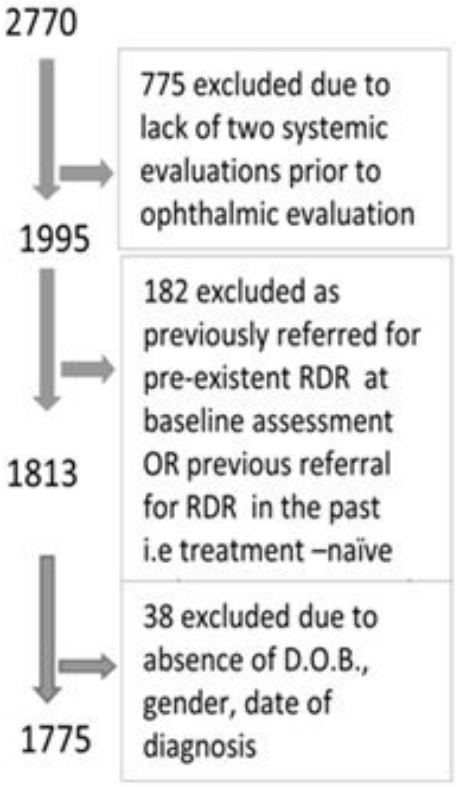
The authors would like to thank the staff at Ophthalmology Department, Mater Misericordiae University Hospital, Eccles St Dublin, Ireland for facilitating the referral cases from

screening in the community. The Authors are very grateful to members of the Research Ethics HSE DNE, especially Dr Brendan McMahon for facilitating the secondary use of clinical data for research purposes and for help with the research ethics application for the study, and to Ms Rosalie Smith-Lynch for all her help and support to this project.

Authors contributions

JJS, DMW, NL conceived and designed the study, with input from PS. DMW, with input from JJS and NL, planned the data analysis. DMW undertook data analysis. JJS, DMW, PS and NL evaluated the results. JJS and NL drafted the first and subsequent versions of the manuscript with input from DMW. JJS, DMW, NL and PS reviewed and approved the final version of the manuscript. NL uploaded the manuscript, reviewed it, and submitted it for publication.

Figure 1: Flow diagram demonstrating total number of participants included in the Diabetes Watch Programme, number of participants included in the model and reasons for exclusion.



D.O.B.= date of birth; RDR = Referable Diabetic Retinopathy

Table 1. Characteristics of people with diabetes type 2 in the entire Diabetes Watch Programme (DWP) cohort (n=2,770) at presentation along with those included in the model or the modelled population (n=1,775).

Patient characteristics	**Modelled cohort n=1,775**		**Entire DW cohort n=2,770**
Demographic	**Category**	**Number (%)**	**Number (%)**
Ethnic Origin	Irish	1,746 (98)	2,723 (98)
	Non-Irish	29 (2)	47 (2)
Gender	Male	1,007 (57)	1,588 (57)
	Female	768 (43)	1,137 (41)
	Gender unknown	0 (0)	45 (2)
Variable			
Baseline Retinal Assessment (ETDRS equivalent)	**Number (%)**		**Number (%)**
R0 (10)	1,378 (78)		1,683 (61)
R1M0 (14 to 35)	259 (15)		304 (11)
U	138 (7.8)		175 (6.3)
	Median (Range)		**Median (Range)**
Age at recruitment into DWP	63 (17, 93)		63 (17, 108)
Duration of diabetes at recruitment(yrs)	2 (0, 47)		0 (0, 72)
	Mean (Standard Deviation)		**Mean (Standard Deviation)**
HbA1c (%)[mmol/mol]	6.8 (1.2) [51]		7.2 (1.6) [55]
BMI (Kg/m^2)	30.8 (6.14)		31 (6.3)
HDl (mmol/l)	1.2 (0.93)		1.3 (1.1)
LDl (mmol/l)	2.3 (0.83)		2.7 (1.1)
Triglycerides (mmol/l)	3.3 (2.3)		3.6 (2.9)
Diastolic BP (mmHg)	77 (9.34)		79 (9.6)
Systolic BP (mmHg)	136 (16.8)		137 (18)

R0 = No retinopathy; R1M0 = Minimal Background Diabetic Retinopathy; U = Unassessable; DWP = Diabetes Watch Programme; .ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = Glycosylated Haemoglobin 1Ac; BMI = Body Mass Index; HDL= High Density Lipoprotein Cholesterol; LDL = Low Density Lipoprotein Cholesterol; BP= Blood pressure; SD = Standard deviation.

Table 2. Risk of referral with referable diabetic retinopathy based on baseline diabetic retinopathy grading and values of systemic risk factors investigated.

Independent Variable	**Hazard Ratio**	**95% CL (lower)**	**95% CL (upper)**	**p value**
Most recently recorded value of variable				
BMI	**0.83**	**0.73**	**0.95**	**0.007**
Systolic BP	**1.29**	**1.15**	**1.45**	**0.001**
Diastolic BP	**0.91**	**0.85**	**0.97**	**0.006**
HbA1c	**1.22**	**1.11**	**1.34**	**0.001**
LDL	1.01	0.89	1.13	0.931
HDL*	1.01	0.97	1.06	0.543
Triglycerides	**1.10**	**1.03**	**1.18**	**0.004**
Rate of change between consecutive measurement of systemic variable				
BMI Rate	0.98	0.95	1.02	0.287
Systolic BP Rate	0.98	0.88	1.09	0.707
Diastolic BP Rate	1.03	0.93	1.14	0.572
HbA1c Rate	0.99	0.94	1.05	0.853
LDL Rate	0.97	0.92	1.03	0.290
Triglycerides Rate	**0.94**	**0.90**	**0.98**	**0.004**
Ophthalmic evaluation result at initial assessment as compared with outcome when initial evaluation result was R0				
Ophthalmic Evaluation (result= R1M0)	**4.02**	**2.80**	**5.78**	**0.001**
Ophthalmic Evaluation (result= R0)	1.0			
Ophthalmic Evaluation (result= U)	1.37	0.75	2.52	0.31

* HDL rate was excluded from the final model as there was strong evidence of collinearity when included.

BP = Blood pressure; HbA1c= Glycosylated haemoglobin A1c; LDL= Low Density Lipoprotein cholesterol; HDL= High Density Lipoprotein cholesterol; BMI = Body Mass Index; R0 = No diabetic retinopathy; R1M0 = Background diabetic retinopathy; U = Unassessable; CL = Confidence Limit.

Table 3. Distribution of current values and rates of change of the variables investigated in the survival model (9,576 systemic evaluations).

Current value of variable	25th percentile	Median	75th percentile
BMI	26.7	30	34
Systolic BP	125	135	145
Diastolic BP	70	79	82
HbA1c%	6.1[43]	6.6[49]	7.4[57]
LDL	1.8	2.2	2.8
HDL	1.0	1.1	1.3
Triglycerides	2.0	2.9	3.8
Rate of change of variable	25th percentile	Median	75th percentile
BMI	-1.4	0	1.2
Systolic BP	-18.4	0	16.7
Diastolic BP	-10.7	0	9.4
HbA1c	-0.6	0	0.6
LDL	-0.6	0	0.5
HDL	-0.2	0	0.2
Triglycerides	-1.6	0	1.5

HbA1c = Glycosylated haemoglobin A1c; LDL= Low Density Lipoprotein cholesterol; HDL = High density lipoprotein cholesterol; BMI = Body Mass Index; BP = Blood Pressure;

References

(1) Wilson J, Jungner G. Principles and practice of screening for disease. Geneva : World Health Organisation(WHO); 1968.

(2) Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bulletin of the World Health Organization 2008;86:241-320.

(3) Rohan T, Frost C, Wald N. Prevention of blindness by screening for diabetic retinopathy; a quantitative assessment. Br Med J 1989;299:1198-1201.

(4) Stefansson E, Bek T, Porta M, Larsen N, Kristinsson J, Agardh E. Screening and Prevention of Diabetic Blindness. Acta Ophthalmol. Scand. 2000;78:374–385.

(5) Screening for Diabetic Retinopathy in Europe – Progress Since 2011 Satellite meeting to EASDec, Manchester 2016 June 23rd 2016.
(http://www.drscreening2005.org.uk/manchester_2016.html).

(6) Diabetic Retinopathy: A Position Statement by the American Diabetes Association. Exams every 2 years may be cost-effective after one or more normal eye exams. Diabetes Care 2017;40:412–418.

(7) Scanlon P., Aldington S., Leal J., Luengo-Fernandez R., Oke J., Sivaprasad S., et al. Development of a cost-effectiveness model for optimisation of the screening interval in diabetic retinopathy screening Health technology assessment. 2015;19(74).

(8) Taylor-Phillips S., Mistry H., Leslie R., Todkill D., Tsertsvadze A., Connock M., et al. Extending the diabetic retinopathy screening interval beyond 1 year: systematic review. Br J Ophthalmol 2016;100:105–114.

(9) Tracey M., McHugh S., Buckley C., Canavan R., Fitzgerald A., Kearney P. Short Report: Epidemiology The prevalence of Type 2 diabetes and related complications in a nationally

representative sample of adults aged 50 and over in the Republic of Ireland . Diabetic Medicine 2016;33:441-445.

(10) Public Health England NHS Diabetic Eye Screening Programme Grading definitions for referable disease http://bmec.swbh.nhs.uk/wp-content/uploads/2013/03/Diabetic-Screening-Service-Revised-Grading-Definitions-November-2012.pdf

(11) Schneider S, Aldington SJ, Kohner EM, Luzio S, Owens DR, Schmidt V et al. Quality assurance for diabetic retinopathy telescreening. Diabet Med. 2005;22:794-802.

(12) Thiébaut, A.C.M., Bénichou, J. 2004. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Statist. Med. 2004;23:3803–3820.

(13) Kohner E., Stratton I., Aldington S., Holman R., Matthews D. Relationship between the severity of retinopathy and progression to photocoagulation in patients with type 2 diabetes mellitus in the UKPDS (UKPDS 52). Diabetes Med 2001;18:178-184.

(14) Stratton I., Aldington S., Taylor D., Adler A., Scanlon P. A Simple Risk Stratification for Time to Development of Sight-Threatening Diabetic Retinopathy. Diabetes Care 2013;36:580–585.

(15) 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;352:837-53.

(16) Stratton I., Adler A., Andrew H., Neil W., Matthews D., Manley S., et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-412.

(17) Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, Matthews DR. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. Diabetologia. 2001;44:156-63.

(18) Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA et al.

Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ. 2000 Aug 12;321:412-9.

(19) Klein B., Klein R., Moss S., Palta M. A Cohort Study of the Relationship of Diabetic Retinopathy to Blood Pressure Arch Ophthalmol. 1995;113:601-606.

(20) Chew E., Davis M., Danis R., Lovato J., Perdue L., Greven C. et al. Action to Control Cardiovascular Risk in Diabetes Eye Study Research Group. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes. Ophthalmology 2014;121:2443-2451.

(21) Do D., Wang X., Vedula S., Marrone M., Sleilati G., Hawkins B., et al. Blood pressure control for diabetic retinopathy. Cochrane Database Syst Rev. 2015 Jan 31;1:CD006127.

(22) Yamamoto M, Fujihara K, Ishizawa M. Osawa T, Kaneko M, Ishiguro H et al. Pulse Pressure is a Stronger Predictor Than Systolic Blood Pressure for Severe Eye Diseases in Diabetes Mellitus. Journal of the American Heart Association 2019:8:e010627

(23) Das R., Kerr R., Chakravarthy U., Hogg R. Dyslipidemia and diabetic macular oedema: a systematic review and meta-analysis. Ophthalmology 2015;122:1820–7.

(24) Jeng CJ, Hsieh YT, Yang CM, Yang CH, Lin CL, Wang IJ. Diabetic Retinopathy in Patients with Dyslipidemia: Development and Progression. Ophthalmol Retina. 2018;2:38-45.

(25) Zhou Y., Zhang Y., Shi K., Wang C. Body mass index and risk of diabetic retinopathy A meta-analysis and systematic review. Medicine (Baltimore) 2017; 96(22):e6754.

(26) Raman R, Rani PK, Gnanamoorthy P, Sudhir RR, Kumaramanikavel G, Sharma T. Association of obesity with diabetic retinopathy: Sankara Nethralaya Diabetic Retinopathy

Epidemiology and Molecular Genetics Study (SN-DREAMS Report no 8). Acta Diabetol 2010;47:209-215.

(27) Lim LS, Tai ES, Mitchell P, Wang JJ, Tay WT, Lamoureux E, Wong TY. C-reactive protein, body mass index, and diabetic retinopathy. Invest Ophthalmol Vis Sci. 2010;51:4458-63.

(28) Dirani M, Xie J, Fenwick E, Benarous R, Rees G, Wong T, et al. Are Obesity and Anthropometry Risk Factors for Diabetic Retinopathy? The Diabetes Management Project. Invest Ophthalmol Vis Sci 2011; 52: 4416–4421.

(29) Aspelund T, Thornórisdóttir O, Olafsdottir E, Gudmundsdottir A, Einarsdóttir AB, Mehlsen J et al. Individual risk assessment and information technology to optimise screening frequency for diabetic retinopathy. Diabetologia. 2011;54:2525-32.

(30) Tracey M., McHugh S., Buckley C., Canavan R., Fitzgerald A., Kearney P. The prevalence of Type 2 diabetes and related complications in a nationally representative sample of adults aged 50 and over in the Republic of Ireland. Diabet Med 2016; 33:441-445.

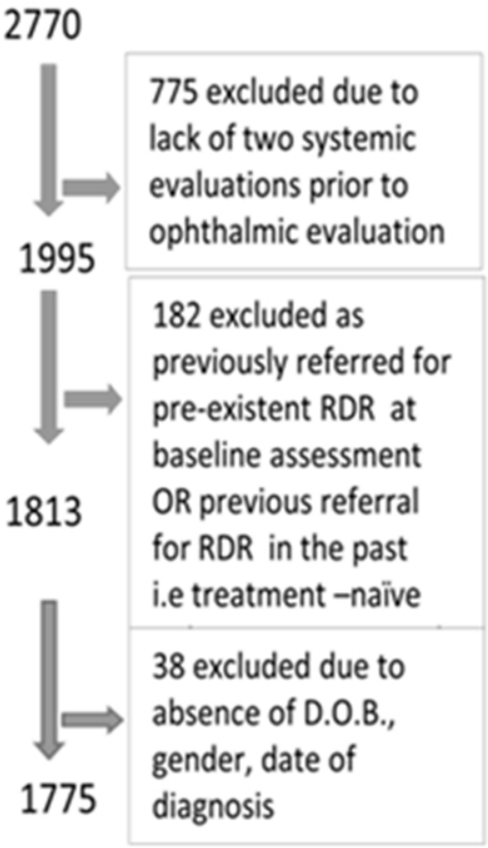


Figure 1: Flow diagram demonstrating total number of patients included in the Diabetes Watch Programme (DWP), number of patients included in the model and reasons for exclusion.

190x254mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ✓
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ✓
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ✓
Objectives	3	State specific objectives, including any prespecified hypotheses ✓
Methods		
Study design	4	Present key elements of study design early in the paper ✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ✓
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ✓ *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed N/A *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ✓
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group ✓
Bias	9	Describe any efforts to address potential sources of bias N/A *
Study size	10	Explain how the study size was arrived at ✓
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ✓
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ✓
		(*b*) Describe any methods used to examine subgroups and interactions ✓
		(*c*) Explain how missing data were addressed ✓
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses N/A

Continued on next page

* ALTHOUGH LIMITATIONS DID REFER TO ONE POTENTIAL SOURCE OF BIAS

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓
		(b) Give reasons for non-participation at each stage	✓
		(c) Consider use of a flow diagram Fig 1	✓
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓
		(b) Indicate number of participants with missing data for each variable of interest	✓
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	✓
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	✓
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses N/A	
Discussion			
Key results	18	Summarise key results with reference to study objectives	✓
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.