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

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What's new?

- In a cohort of people with type 2 diabetes in the Republic of Ireland, mild retinopathy, when compared with no retinopathy, at screening was strongly associated with increased risk of progression to referable retinopathy.
- Elevated HbA_{1c}, systolic blood pressure and triglyceride levels were associated with increased risk of referral.
- Elevated 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 the strength of their association with incidence/progression of retinopathy is essential if individualized risk-based screening programmes are to be implemented.

Abstract

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

Research design and methods The study was conducted in a dynamic cohort of 2770 people with type 2 diabetes, recruited between April 2005 and July 2013. Systemic factors (systolic and diastolic blood pressure, HbA_{1c}, lipid levels, BMI) and baseline diabetic retinopathy grading results were evaluated at 4-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 fourfold increased risk of progression to referral when retinopathy was present at baseline vs no retinopathy at baseline (hazard ratio 4.02, 95% CI 2.80–5.78; *P*<0.001). Higher current values of HbA_{1c} (hazard ratio 1.22, 95% CI 1.11–1.34; *P*<0.001), systolic blood pressure (hazard ratio 1.29, 95% CI 1.15–1.45; *P*<0.001) and triglycerides (hazard ratio 1.10, 95% CI 1.03–1.18; *P*=0.004) were associated with increased risk of referral. Higher current BMI (hazard ratio 0.83, 95% CI 0.73–0.95; *P*=0.007) and diastolic blood pressure (hazard ratio 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 the criteria set by Wilson and Jungner [1], later adopted by the WHO [2], to justify screening for a disease. Screening for DR and timely treatment of its complications, diabetic macular oedema and proliferative DR, prevents more than 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 evaluation 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 and there is increased life expectancy and improved diabetic control. The American Diabetes

Association advised extending the interval between screening episodes for people with well-controlled type 2 diabetes and no DR at the most recent evaluation [6]. In 2015, a health technology assessment concluded that if a risk model is employed with personalized 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 people with type 2 diabetes with low risk [8].

The risk of a person with type 2 diabetes progressing to referable DR and potentially sight-threatening DR (i.e. diabetic macular oedema and/or proliferative DR) between two consecutive ophthalmic evaluations, which would indeed determine the appropriate screening interval, appears dependent on multiple risk factors, local and systemic. Establishing these in different populations is essential if personalized screening intervals are to be introduced.

The present study provides insight into the risk factors for development of referable DR in the Irish population, for whom very sparse data have been available to date.

Participants and methods

Participants

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 type 2 diabetes aged ≥ 18 years registered with 20 general practices. Diagnosis and assessments adhered to established methods [9]. People with type 1 diabetes and prediabetes and those currently accessing secondary care for type 2 diabetes-related (other than ophthalmic) complications were excluded.

Between February 2005 and December 2007, 1265 individuals with pre-existing type 2 diabetes were recruited to the Diabetes Watch Programme. Subsequently, between February 2008 and July 2013, targeted screening of asymptomatic individuals identified 1505

people with newly diagnosed type 2 diabetes in the same general practices. All 2770 people were enrolled in the Diabetes Watch Programme.

Systemic and ophthalmic evaluations

Systemic evaluations were undertaken at 4-month intervals by specialist nurses. Visits were combined with structured education. Systolic and diastolic blood pressure, HbA_{1c}, serum lipids and 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 on continued attendance at systemic evaluations in primary care. Retinal imaging was undertaken by trained technicians at or near the general practice within fixed or mobile screening services on an annual basis. For each eye, best-corrected LogMAR (logarithm of the minimum angle of resolution) 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. those with inoperable media opacity) or with previously identified sight-threatening DR, were assigned an ophthalmological examination using slit-lamp biomicroscopy.

Image grading

In accordance with the recommendations of the English National Screening Programme for Diabetic Retinopathy [10], image grading was a three-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 English National Screening Programme for Diabetic Retinopathy 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 (proliferative DR) 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 diabetic macular oedema, 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). Participants graded as R1 M1, R2 M0, R2 M1, R3 M0 or R3 M1 in one or 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).

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 variables over time (e.g. decreases in HbA_{1c} as participants 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. hazard ratio). 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: the most recently recorded value and 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 timescale and thus modelled implicitly [12].

All quantitative measurements were standardized 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 hazard ratios 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: most recently recorded values of systemic variables; rates of change between consecutive measurements in systemic variables; and retinopathy grading at initial assessment.

Ethics approval

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

Results

A total of 2770 people with type 2 diabetes were included. During the 8-year period of the programme, 9604 ophthalmic evaluations occurred, which were linked to 22 701 systemic evaluations, of which 19 172 (84%) had complete data for all variables selected. Of the initial total, 1770 people were eligible to be included in the Cox proportional hazards model (Fig. 1) aimed at estimating risk of developing referable DR. A total of 9576 systemic evaluations were conducted on the modelled cohort during follow-up and were included in the survival analysis. A total of 143 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 [hazard ratio 4.02, 95% CI 2.80–5.78; $P < 0.001$ (Table 2)].

Higher values of the most recently recorded HbA_{1c} concentration (hazard ratio 1.22, 95% CI 1.11–1.34; P=0.001), systolic blood pressure (hazard ratio 1.29, 95% CI 1.15–1.45; P=0.001) and triglycerides (hazard ratio 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 [hazard ratio 0.94, 95% CI 0.90–0.98; P=0.004 (Table 2)]. High current BMI (hazard ratio 0.83, 95% CI 0.78–0.95; P=0.007) and diastolic blood pressure (hazard ratio 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 HbA_{1c}, systolic blood pressure and triglycerides were all associated with increased risk of developing referable DR, whereas high BMI and diastolic blood pressure 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 fourfold increased risk in people in the R1 M0 group when compared with those in the R0 M0 group.

The stage of DR appears to be a major determinant of risk of DR progression. In the UK Prospective Diabetes Study (UKPDS), a randomized clinical trial that examined the effect of tight glycaemic control in people with type 2 diabetes, 0.2% and 2.6% of people with no retinopathy at baseline [R0/Early Treatment Diabetic Retinopathy Study (ETDRS) grade 10] required laser treatment at 3 and 9 years, respectively, when compared with 15% and 32% for those with mild to moderate non-proliferative DR (R2/ETDRS grades 35–43) [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 1 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 1 year later, the risk of subsequent sight-threatening DR was ~18 times higher than if there was no retinopathy in either eye at both assessments. In agreement with these findings, in the population of the Diabetes Watch Programme in the Republic of

Ireland, early signs of DR in people with type 2 diabetes 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, HbA_{1c}, is a well-recognized risk factor for development and progression of DR in people with type 2 diabetes [15–17]. In the UKPDS [16], for every percentage HbA_{1c} point reduction (e.g. from 8% to 7%, i.e. 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 HbA_{1c} 51 mmol/mol (6.8%)], the deleterious effect of HbA_{1c} 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 blood pressure in the development and progression of DR is less clear. In the UKPDS, intensive treatment reduced the incidence of DR [18]; however, no consistent association was observed in the Wisconsin Epidemiological Study of Diabetic Retinopathy [19], in which high systolic blood pressure was a significant risk factor for development of DR only in people with younger-onset diabetes (onset <30 years of age) and 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 blood pressure did not significantly affect DR progression. A systematic review and meta-analysis revealed that intensive control of blood pressure had preventive effects on 4–5-year 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 blood pressure on incidence/progression of DR may relate to different baseline levels of blood pressure in different populations (e.g. in intervention studies, if the levels of blood pressure at study entry were only mildly elevated, reducing the blood pressure 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). Interestingly, in the Diabetes Watch Programme cohort, higher diastolic blood pressure appeared protective. It could be speculated that the elevated diastolic blood pressure in people with high systolic blood pressure would reduce pulse pressure [22] which, in turn, would have a positive effect, reducing shear forces in retinal blood vessel walls, and 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 type 1 and type 2 diabetes found mean levels of serum triglycerides to be significantly higher in those with diabetic macular oedema than in those without [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 diabetic macular oedema, as referable DR included R2 and R3 (proliferative DR) in addition to diabetic macular oedema. 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 dyslipidaemia on the incidence of DR, diabetic macular oedema and proliferative DR [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, as 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 is used to assess abdominal obesity and visceral fat; the correlation between BMI and

waist to hip ratio 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 HbA_{1c} and systolic blood pressure 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 blood pressure in the Irish population, as a result of the present findings of the Diabetes Watch programme).

Future studies evaluating risk factors should examine them differentially for diabetic macular oedema and proliferative DR (rather than together, under umbrella terms of 'referable DR' or 'sight-threatening DR'), given that the consequences of diabetic macular oedema and proliferative DR are different. Diabetic macular oedema does not cause rapid visual loss or affect peripheral vision, unlike proliferative DR which, if accompanied by contraction of the posterior hyaloid face and pre-retinal fibrosis, can rapidly progress to

tractional retinal detachment and loss of central and peripheral vision. It should be noted, however, that although most people with diabetes, if not all, will develop DR at some point in their lives, progression from mild non-proliferative DR to more severe stages may not always occur. Furthermore, in only a small proportion of people with DR, diabetic macular oedema or proliferative DR 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 type 2 diabetes 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 participants in the present cohort may represent the wider diabetic population well. 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 developed referable DR during the follow-up). Furthermore, the categorization of referable DR, as used in this study, hindered our ability to look separately for risk factors for diabetic macular oedema or proliferative DR, and may have disguised associations with one or the other which may have been revealed if these

entities had been studied separately. Strengths include the standardized 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.

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Competing interests

None declared.

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FIGURE 1 Flow diagram showing the total number of participants included in the Diabetes Watch Programme, the number of participants included in the model and reasons for exclusion. D.O.B., date of birth; RDR, referable diabetic retinopathy.

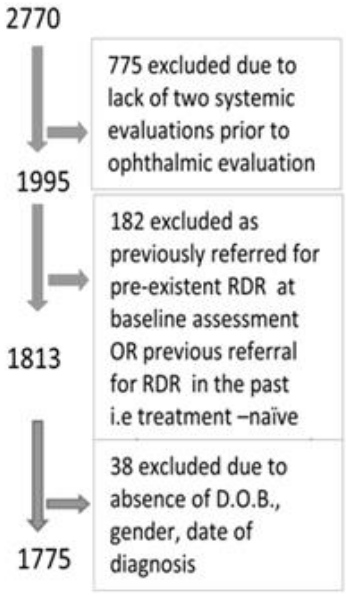

Table 1 Characteristics of people with type 2 diabetes in the entire Diabetes Watch Programme cohort (*N*=2770) at presentation, along with those included in the model or the modelled population (*N*=1775)

Patient characteristic	**Modelled cohort *N*=1775**	**Entire DWP cohort *N*=2770**
Ethnic origin, *n* (%)		
Irish	1746 (98)	2723 (98)
Non-Irish	29 (2)	47 (2)
Men, *n* (%)	1007 (57)	1588 (57)
Women, *n* (%)	768 (43)	1137 (41)
Gender unknown, *n* (%)	0 (0)	45 (2)
Baseline retinal assessment (ETDRS equivalent) , *n* (%)		
R0 (10)	1378 (78)	1683 (61)
R1M0 (14 to 35)	259 (15)	304 (11)
U	138 (7.8)	175 (6.3)
Median (range) age at recruitment into DWP	63 (17–93)	63 (17–108)
Median (range) duration of diabetes at recruitment, years	2 (0–47)	0 (0–72)
HbA_{1c}		
mmol/mol	51	55
%	6.8 (1.2)	7.2 (1.6)
BMI, kg/m^2	30.8 (6.14)	31 (6.3)
HDL cholesterol, mmol/l	1.2 (0.93)	1.3 (1.1)
LDL cholesterol, mmol/l	2.3 (0.83)	2.7 (1.1)
Triglycerides, mmol/l	3.3 (2.3)	3.6 (2.9)

Diastolic blood pressure, mmHg	77 (9.34)	79 (9.6)
Systolic blood pressure, mmHg	136 (16.8)	137 (18)

DWP, Diabetes Watch Programme; ETDRS, Early Treatment Diabetic Retinopathy Study; R0, no retinopathy; R1 M0, minimal background diabetic retinopathy; U, unassessable.

Values are mean (SD), unless otherwise indicated.

Table 2 Risk of 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***
Most recently recorded value of variable				
BMI	**0.83**	**0.73**	**0.95**	**0.007**
Systolic blood pressure	**1.29**	**1.15**	**1.45**	**0.001**
Diastolic blood pressure	**0.91**	**0.85**	**0.97**	**0.006**
HbA_{1c}	**1.22**	**1.11**	**1.34**	**0.001**
LDL cholesterol	1.01	0.89	1.13	0.931
HDL cholesterol*	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	0.98	0.95	1.02	0.287
Systolic blood pressure	0.98	0.88	1.09	0.707
Diastolic blood pressure	1.03	0.93	1.14	0.572
HbA_{1c}	0.99	0.94	1.05	0.853
LDL cholesterol	0.97	0.92	1.03	0.290
Triglycerides	**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= R1 M0)	**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

CL, confidence limit; R0, no diabetic retinopathy; R1M0, background diabetic retinopathy; U, unassessable.

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

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 blood pressure	125	135	145
Diastolic blood pressure	70	79	82
HbA_{1c}			
mmol/mol	43	49	57
%	6.1	6.6	7.4
LDL cholesterol	1.8	2.2	2.8
HDL cholesterol	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 blood pressure	–18.4	0	16.7
Diastolic blood pressure	–10.7	0	9.4
HbA_{1c}	–0.6	0	0.6
LDL cholesterol	–0.6	0	0.5
HDL cholesterol	–0.2	0	0.2
Triglycerides	–1.6	0	1.5