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RESEARCH

Incidence of diabetic retinopathy in people with type 2 diabetes mellitus attending the Diabetic Retinopathy Screening Service for Wales: retrospective analysis

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Abstract

Objectives To determine the incidence of any and referable diabetic retinopathy in people with type 2 diabetes mellitus attending an annual screening service for retinopathy and whose first screening episode indicated no evidence of retinopathy.

Design Retrospective four year analysis.

Setting Screenings at the community based Diabetic Retinopathy Screening Service for Wales, United Kingdom.

Participants 57 199 people with type 2 diabetes mellitus, who were diagnosed at age 30 years or older and who had no evidence of diabetic retinopathy at their first screening event between 2005 and 2009. 49 763 (87%) had at least one further screening event within the study period and were included in the analysis.

Main outcome measures Annual incidence and cumulative incidence after four years of any and referable diabetic retinopathy. Relations between available putative risk factors and the onset and progression of retinopathy.

Results Cumulative incidence of any and referable retinopathy at four years was 360.27 and 11.64 per 1000 people, respectively. From the first to fourth year, the annual incidence of any retinopathy fell from 124.94 to 66.59 per 1000 people, compared with referable retinopathy, which increased slightly from 2.02 to 3.54 per 1000 people. Incidence of referable retinopathy was independently associated with known duration of diabetes, age at diagnosis, and use of insulin treatment. For participants needing insulin treatment with a duration of diabetes of 10 years or more, cumulative incidence of referable retinopathy at one and four years was 9.61 and 30.99 per 1000 people, respectively.

Conclusions Our analysis supports the extension of the screening interval for people with type 2 diabetes mellitus beyond the currently recommended 12 months, with the possible exception of those with diabetes duration of 10 years or more and on insulin treatment.

Introduction

Diabetic retinopathy remains a major cause of visual impairment and blindness in the United Kingdom,[1] with its early detection and timely treatment[2-4] capable of reducing the risk of visual loss. The evidence that screening for diabetic retinopathy is cost effective[5 6] has led to the establishment, over the past 20 years, of several screening programmes at local, regional, and national levels throughout the UK and elsewhere, varying in size, design, and complexity.[7 8]

Various methods have been used to screen for diabetic retinopathy, including ophthalmoscopy (direct and indirect);[9] obtaining retinal images (for example, Polaroid images),[9-11] 35 mm transparencies,[12] and more recently digital images with[13] or without mydriasis;[14 15] as well as combining ophthalmoscopy with retinal photography.[16 17] In 1999, the National Screening Committee for England and Wales recommended the use of digital photography through dilated pupils to screen people for diabetic retinopathy[18 19] from the age of 12 years. A national consensus protocol for grading and disease management, based on annual screening,[20] was also developed as part of the yearly review for every person with diabetes. In 2003, the Diabetic Retinopathy Screening Service for Wales was established and is currently responsible for the annual screening of 150 000 people registered with diabetes mellitus in Wales (about 5% of the population).

Despite the increase in diabetes mellitus worldwide,[21] some evidence has suggested a decline during the past few decades in the prevalence and incidence of diabetic retinopathy,

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especially sight threatening retinopathy. This reduction is attributed not only to improved care but also to the earlier detection of both diabetes and diabetic retinopathy.[22-24] Evidence from screening programmes of relatively small numbers of patients with type 2 diabetes has also suggested that an extension of the screening interval—beyond the currently recommended 12 months—would be safe for those without evidence of retinopathy at first screening.[25-29] Such a change in policy could substantially reduce heath service expenditure while allowing reinvestment into the screening service. This reinvestment could provide more frequent screening for people with early exudative maculopathy and early diabetic retinopathy, and allow earlier discharge of patients at the hospital eye service as a result of more frequent follow-up being available at the screening service.

Our study reviewed data for a large population of people with type 2 diabetes mellitus who had shown no evidence of diabetic retinopathy at their first screen. We estimated the annual and cumulative incidence of retinopathy over a four year period, and explored the association between the development of retinopathy and its putative risk factors.

Methods

Study population

Every person known to have diabetes mellitus over the age of 12 years and registered with a general practice in Wales must be referred to the Diabetic Retinopathy Screening Service for Wales by their doctor, apart from those excluded on medical grounds (for example, those unable to attend screening owing to infirmity or comorbidity)[30] or those already attending hospital based ophthalmology services because of retinopathy. Our four year retrospective analysis included data for all patients classified as having type 2 diabetes mellitus, diagnosed over the age of 30 years, and who attended screening between January 2005 and November 2009. Exclusion criteria included: a diagnosis, on referral to the screening service, of type 1 diabetes mellitus; a diagnosis of type 2 diabetes mellitus but at age younger than 30 years; or no type of diabetes mellitus recorded on the referral notification (predominantly from primary care). Data were anonymised before undergoing statistical analysis.

Screening procedure

After registration with the Diabetic Retinopathy Screening Service for Wales, each patient is invited to attend screening at a location closest to them (with an appointment date and time). Screening is undertaken at a variety of venues throughout Wales, including general practice surgeries and local hospitals or community centres. A trained healthcare assistant assesses patients' current visual acuity in both eyes (achieved with or without glasses or with pinhole reading), using an illuminated 3 m Snellen chart. Tropicamide (1%) is then applied to each eye, and after about 15 minutes, a trained photographer takes two 45° digital retinal images per eye (one macular centred, and one nasal field) using a non-mydriatic Canon DGi camera (with a 30D or 40D camera back). The retinal images are transferred to a central reading centre for grading. The photographers can also take additional images of the retina, lens, or iris if deemed necessary.

Diabetic retinopathy grading

Trained staff use a standardised protocol to grade diabetic retinopathy, which is an enriched version of the English National Screening Protocol,[20] and take the worst grade for either eye as the final grading level. We used the following grading categories of retinopathy: none present, background, preproliferative or proliferative, and maculopathy (based on surrogate markers such as exudates within 1 disc diameter of the fovea).

For the statistical analysis, we defined referable retinopathy as participants with preproliferative or proliferative retinopathy (with or without maculopathy), or maculopathy with background retinopathy. This category relates to those who would, according to guidelines, need referral to the hospital eye service for further assessment or treatment. Digital retinal images were not considered gradable if the retina of both eyes could not be visualised adequately—that is, retinal vessels were not visible within 1 disc diameter of the centre of the fovea and fine vessels were not visible across the surface of the optic disc.

Ethical approval

We sought advice from the South East Wales research ethics committee, as well as from the Cardiff and Vale University Health Board (previously the Cardiff and Vale National Health Service trust), the host organisation for the Diabetic Retinopathy Screening Service for Wales, on behalf of the Welsh Assembly Government. In their considered opinion, this study was a service evaluation and therefore did not require ethical approval. Individual patients provided written informed consent at each screening event for their anonymised data to be used in research.

Statistical analysis

We used descriptive analyses to characterise the study population and patterns of diabetic retinopathy, and used *t* tests and χ^2 tests to explore differences between patients without any retinopathy and those who developed any, background, or referable retinopathy. Parametric survival analysis with covariates identified those factors associated with the development of referable retinopathy.

The presence or absence of diabetic retinopathy was determined after each screening event during the study period. Although intended to occur annually, screening took place at variable times during the four year period. For people who developed retinopathy between two screening events, the time to development lay between the two episodes, and therefore the data were interval censored; for those who did not develop the disorder by the final screening event, the data were right censored. We therefore modelled the time to development of retinopathy using survival analysis to allow for these two types of censoring.

We used a parametric approach, implemented by the routine INTCENS program in Stata. From the estimated parameters, the survival function was calculated to derive the annual and cumulative incidence of any and referable diabetic retinopathy. We used bootstrapping to calculate confidence intervals, because we could not obtain the standard errors easily.[31] Different distributions were considered for the underlying survival times, including Weibull, exponential, Gompertz, log normal, and inverse Gaussian. We chose the distribution on the basis of the Akaike information criterion.[32]

We explored the effect of putative risk factors with available information (that is, age, sex, age at diagnosis, duration of diabetes mellitus, and treatment types) by incorporating them into this survival analysis. To avoid assumptions of linearity, we used the following categories for the duration of diabetes: less than five years, five to nine years, and 10 years or more. Age categories were: 30-49 years, 50-59 years, and 70 years or older. The risk factors were examined individually and then re-examined in a multivariate analysis with all variables included. We did statistical analyses using SPSS version 16 and

Stata version 10; evidence of significance was taken as P<0.05 unless otherwise stated.

Results

A total of 85 214 individuals with type 2 diabetes mellitus underwent screening for diabetic retinopathy between January 2005 and November 2009; 57 199 (67.1%) had no evidence of retinopathy and were therefore eligible for inclusion in this study. At the initial screening event, 22 501 (26.4%) had evidence of background retinopathy and 3723 (4.4%) had referable retinopathy. Those with referable retinopathy consisted of: 1169 (1.4%) with maculopathy, 1279 (1.5%) preproliferative retinopathy, and 262 (0.3%) proliferative retinopathy (817 (1.0%) preproliferative retinopathy and maculopathy, 196 (0.2%) proliferative retinopathy and maculopathy). We excluded 1791 (2.1%) participants who had images that could not be graded, as well as those with evidence of existing retinopathy.

Of 57 199 people without evidence of diabetic retinopathy at the first screening event, 7436 (13.0%) did not attend another screening during the study period, 449 (6.0%) of whom were not eligible for a second screen (which would have occurred within 12 months). We do not know why the remaining 6987 (94.0%) people did not attend a second screening event, because anonymisation of the records prevented further investigation; however, this group was older and had a longer known duration of diabetes than the group attending at least one additional screening event (table 1⇓). We did not observe a significant difference in the proportions of male participants between these two groups.

We found that 49 763 participants had a second screening event, 31 924 (64.2%) a third, 10 615 (21.3%) a fourth, and 767 (1.5%) a fifth (total of 93 069 events). Although screening was intended to occur annually, the screening intervals were generally longer than one year, with a mean (standard deviation) interval of 17.8 (6.3) months between the first and second screening events, 15.3 (4.4) months between the second and third, 13.2 (2.7) months between the third and fourth, and 12.0 (1.9) months between the fourth and fifth. Only 4479 (9%) participants had an interval of 12 (1) months between screening events.

During the study, 12 922 (26.0%) participants with type 2 diabetes mellitus developed diabetic retinopathy, of whom the vast majority (12 574 (97.3%)) developed background retinopathy. Of 348 (0.7%) people who developed referable retinopathy, 197 (56.6%) had evidence of maculopathy, 107 (30.7%) had preproliferative retinopathy, and 25 (7.2%) proliferative retinopathy. Sixteen (4.6%) people had preproliferative retinopathy and maculopathy, and three (0.9%) had proliferative retinopathy and maculopathy.

Of 28 participants who developed proliferative diabetic retinopathy (with or without maculopathy), 14 (50.0%) did so between 12 and 24 months after the first screening event, three (10.7%) after 24-36 months, 10 (35.7%) after 36-48 months, and one (3.6%) after 48 months. Duration of diabetes was less than five years in 19 (68%) participants, and 27 (96%) received diet and oral treatment, with only one receiving insulin. Of participants who developed proliferative retinopathy within 12 to 24 months, none were on insulin treatment and only two (14%) had had diabetes longer than 10 years.

In the survival analysis, we selected the Weibull distribution as best fitting the data. Tables 2⇓ and 3⇓ show the estimated annual and cumulative incidence of any and referable diabetic retinopathy. The annual incidence of any retinopathy at one year was 124.94 per 1000 people, decreasing to 66.59 per 1000 at four years, with a cumulative incidence of 360.27 per 1000 people at four years. By contrast, the annual incidence of referable retinopathy increased from 2.02 to 3.54 per 1000 people, with a cumulative incidence of 11.64 at four years. The cumulative incidence of each retinopathy group was about twice as high in participants who received insulin treatment (tables 2 and 3).

Table 4⇓ summarises the baseline characteristics of the three groups according to outcome—that is, participants who did not develop diabetic retinopathy and those who developed any or referable retinopathy. The mean known duration of diabetes mellitus and the proportion of participants requiring insulin treatment were significantly greater in those who developed referable retinopathy than in those who remained free of retinopathy. Mean ages at diagnosis of diabetes and at first screening were lowest in the group that developed referable retinopathy and highest in the group that did not develop any retinopathy. Sex distribution did not differ between the groups.

Table 5⇓ shows the effects of putative risk factors on the risk of participants developing diabetic retinopathy. A significantly raised risk of referable retinopathy was associated with an increased duration of diabetes mellitus. Risk was highest in participants diagnosed at age 30-49 years, with significantly reduced risks in those aged up to 70 years at diagnosis. The risk of any or referable retinopathy varied greatly between different types of diabetes treatment. Age, duration of diabetes, and treatment had similar effects on the risk of developing background retinopathy, although age at diagnosis of more than 70 years was associated with a significantly increased risk.

The incidence of referable retinopathy varied considerably between subgroups. For example, for participants given diet treatment only with a known duration of diabetes of less than five years, the cumulative incidence of retinopathy at one, two, and three years from the first negative screen was 1.83, 3.66, and 5.45 per 1000 people, respectively. Corresponding values for participants receiving insulin treatment with a duration of diabetes of less than 10 years were 0.71, 3.80, and 10.10 per 1000 people, respectively. For participants with a duration of diabetes of 10 years or more, the use of insulin treatment increased cumulative incidence greatly (with insulin treatment 2.24, 5.86, and 10.33 per 1000 people; without insulin treatment 9.61, 17.10, and 24.26 per 1000 people).

Discussion

In our study relating to people with type 2 diabetes mellitus enrolled in the national Diabetic Retinopathy Screening Service for Wales from 2005 to 2009 with no evidence of diabetic retinopathy at initial screening, the annual incidence of any retinopathy per 1000 people was 124.94 (12.5%) in the first year, falling each year to 66.59 (6.7%) in the fourth year. The cumulative incidence at four years was 360.27 per 1000 people (36.0%). The annual incidence of referable retinopathy per 1000 people was low at 2.02 (0.2%) in the first year, with a small increase to 3.54 (0.4%) in the fourth year; the cumulative incidence at four years was 11.64 (1.2%).

The incidence of referable retinopathy was positively and independently associated with the known duration of type 2 diabetes and the need for insulin treatment, and inversely related to age at diagnosis. For participants on diet treatment with a duration of diabetes of less than five years, the cumulative incidence of referable diabetic retinopathy at one, two, and three years was 1.83, 3.66, and 5.45 per 1000 people, respectively. By contrast, the corresponding values for participants using insulin treatment with a duration of diabetes of more than 10 years were 9.61, 17.10, and 24.26 per 1000 people, respectively,

an approximately fivefold increase. For participants not using insulin with a duration of diabetes of more than 10 years, the corresponding values were 2.24, 5.86, and 10.33 per 1000 people, respectively, and 0.71, 3.80, and 10.10 per 1000 people, respectively, for those using insulin treatment with a duration of diabetes of less than 10 years.

The results suggest that for people with type 2 diabetes mellitus and no evidence of retinopathy at screening, the interval of screening could be extended beyond the 12 months currently (but rarely) adopted. Patients on insulin treatment with a history of diabetes of 10 years or more should continue to be screened annually.

Strengths and weaknesses of the study

The large sample size was one of the main strengths of this study. Furthermore, all participants were screened for the presence of retinopathy by a standardised protocol of digital retinal imaging and subsequent grading by trained staff. However, screening was restricted to two 45° retinal images per eye, and only limited information was available on putative risk factors for the development of diabetic retinopathy (we could not obtain measures of glycaemic control, blood pressure, and lipid concentrations). We recorded a high dropout rate (12%) of participants who did not have a second screening event despite being eligible. We were not able to obtain information for those people who did not participate in screening; some may have been excluded for medical reasons, because they were already receiving care from an ophthalmologist for diabetic retinopathy, or they did not attend for other unknown reasons.

Comparison with other studies

The annual incidence of referable diabetic retinopathy observed in our study was similar to that previously reported by Younis and colleagues from the Liverpool Diabetic Eye screening programme for sight threatening retinopathy (equivalent to our category of referable retinopathy)—0.2% in the first year, with a cumulative incidence of 1.7% at four years.[26] The authors recommended an extension of the screening interval to triennial screening, based on the 95% probability of people remaining free from sight threatening retinopathy with a mean screening interval of 5.4 years.

Data from the annual screening programme in Norfolk[28] and the biennial screening programme in Iceland[25] also concluded that biennial screening intervals would be safe in those people without evidence of diabetic retinopathy at screening. The Icelandic screening programme reported that people who developed sight threatening retinopathy were placed on annual screening once they were identified as having background retinopathy. Therefore, these patients had no undue delay in the diagnosis or treatment of sight threatening retinopathy over the 10 year period of observation.[25]

A study of the Swedish screening programme used a three year screening interval in a cohort of well controlled participants (mean HbA_{1c} 6.4% at baseline) with type 2 diabetes mellitus, who showed no evidence of retinopathy and had a mean known duration of diabetes of six years.[29] The researchers observed that 28% of participants developed mild to moderate retinopathy, but did not develop sight threatening or referable retinopathy in the form of severe preproliferative or proliferative retinopathy during the three year study period. However, they did identify macular oedema in three people, one of whom needed laser treatment.

Several studies, including the Liverpool Diabetic Eye Study,[26] similarly found that the incidence of diabetic retinopathy was associated with the duration of diabetes and the use of insulin treatment.[33-36] A younger age at diagnosis of diabetes has also been linked with increased incidence of retinopathy,[33] although this association was not found in the UK Prospective Diabetes Study.[37] In agreement with previous studies,[26 37] we found no relation between the incidence of retinopathy and participants' sex, but we found a strong association between incidence and the use of insulin treatment, presumably indicating the stage of the disease.

Therefore, on the present evidence, annual screening is not necessary for people with type 2 diabetes with no lesions of diabetic retinopathy seen on digital images. Exceptions would include people with a duration of diabetes of 10 years or more and on insulin treatment, who should be retained on annual screening. If the screening service used a screening interval longer than 1 year, it would need to use safeguards to ensure that if patients changed risk groups within the year, a new appropriate interval would apply. Safeguards would include the education of patients and professionals to be aware of signs or symptoms suggestive of sight threatening retinopathy, and robust communication between healthcare professionals and the screening service. As electronic patient records become more widespread, these objectives could be more readily achievable.

Not all people classified as having referable diabetic retinopathy, for the purpose of screening, need urgent treatment at the first ophthalmological review. This is because most of these referrals are for isolated exudates (exudative maculopathy) without associated leakage (macular oedema) and early preproliferative retinopathy that need further investigations with fluorescein angiography or optical coherence tomography to determine high risk features. Laser treatment for such changes is not indicated, according to the Early Treatment of Diabetic Retinopathy Study,[3] although focal laser treatment is considered for clinically important macular oedema. Early preproliferative retinopathy is also generally not treated in the first instance, since such cases are monitored for progression to high risk features and sometimes these retinal signs can resolve with improvement of glycaemic control.

The decision to treat is based on various factors, such as severity and status of the fellow eye, diabetes control, blood pressure, and lipid status. Clearly, if proliferative diabetic retinopathy is evident, early treatment with pan retinal photocoagulation can prevent the loss of vision.[2] A delay in diagnosing early exudative maculopathy or preproliferative retinopathy should not necessarily result in a poor outcome, since most diagnosed patients would enter a period of observation by the ophthalmologist after referral.

Future research

Our future research will explore the implications of varying the screening interval using risk stratification. To better predict the development of retinopathy, further research should investigate additional risk factors (for example, the individual and collective effects of glycaemic control (HbA_{1c}), blood pressure, albumin excretion, and lipid status, as well as possible treatments). These findings could improve risk stratification by better defining safe screening intervals on an individual basis. Another important area to investigate further includes the economic effect of the different screening intervals.

Conclusion and implications for policy makers

Other screening programmes have been able to revise their screening intervals based on evidence—that is, cervical,[38]

breast,[39] and bowel[40] screening programmes in the UK. The original recommendation to undertake annual screening for diabetic retinopathy was based on a consensus view of experts and the over-riding wish to include such findings as part of the annual review for people with diabetes. Much debate has surrounded the appropriate screening interval for retinopathy screening, and although the American Diabetes Association recently recommended yearly screening, it suggested less frequent screening in people with at least one previous negative screen.[41]

Our study shows that the annual incidence of referable diabetic retinopathy is low in people with type 2 diabetes mellitus and without evidence of retinopathy at initial screening. These results lend further support to the suggestion of an extension to the screening interval beyond the 12 months currently adopted (although rarely achieved), with the possible exception of patients with a known duration of diabetes of longer than 10 years and on insulin treatment, who should continue to be screened annually. People who develop background retinopathy should also continue annual screening to avoid any delay in referral to ophthalmology services should sight threatening retinopathy develop, as adopted by the Icelandic screening service.[25]

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Data sharing: No additional data available

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What is already known on this topic

Screening for diabetic retinopathy is cost effective

Diabetic retinopathy remains the leading cause of blindness in the working age population

Previous studies have questioned the need for annual screening

What this study adds

For people with type 2 diabetes mellitus with no evidence of diabetic retinopathy at initial screening, the interval of screening could be extended beyond the 12 months currently adopted, but rarely achieved. Possible exceptions are patients with a history of diabetes of 10 years or more and on insulin treatment, who should continue to be screened annually

Future research should focus on a more comprehensive risk stratification as a basis for defining safe screening intervals

Tables

Table 1| Baseline characteristics of study participants

Characteristics	Participants without evidence of diabetic retinopathy at initial screening		P
	Did not attend a further screening event (n=6897)*	Attended at least one further screening event (n=49 763)	
Age (years)†	66.9 (13.5)	64.4 (11.3)	<0.001
Known duration of diabetes mellitus (years)†	4.6 (4.8)	4.2 (4.4)	<0.001
Age at diagnosis of diabetes mellitus (years)†	62.3 (13.2)	60.2 (11.3)	<0.001
Sex‡			
Male	3794 (55.0)	27 529 (55.3)	0.087
Female	3175 (46.0)	21 975 (44.2)	
Unknown	18 (0.3)	259 (0.5)	
Treatment for diabetes mellitus‡			
Diet	2684 (38.9)	17 236 (34.6)	<0.001
Oral hypoglycaemic agents	3787 (54.9)	29 049 (58.4)	
Insulin	394 (5.7)	2669 (5.4)	
Unknown	122 (1.8)	809 (1.6)	

*Group includes eligible participants only. †Mean (standard deviation). ‡Number (%).

Table 2| **Yearly incidence of any and referable diabetic retinopathy in participants without retinopathy at baseline**

Time from last negative screen	Any retinopathy		Referable retinopathy	
	Annual incidence	Cumulative incidence	Annual incidence	Cumulative incidence
1 year	124.94 (120.62 to 128.32)	124.94 (120.62 to 128.32)	2.02 (1.63 to 2.44)	2.02 (1.63 to 2.44)
2 years	91.68 (89.67 to 93.66)	216.81 (211.50 to 220.04)	2.82 (2.51 to 3.12)	4.85 (4.29 to 5.43)
3 years	76.96 (74.96 to 79.30)	293.80 (287.34 to 297.76)	3.24 (2.76 to 3.68)	8.09 (7.20 to 8.93)
4 years	66.59 (64.67 to 68.92)	360.27 (352.98 to 366.06)	3.54 (2.89 to 4.21)	11.64 (10.27 to 13.00)

Data are incidence (95% confidence interval) per 1000 people. Incidence of background retinopathy is the difference between the incidences of any and referable retinopathy.

Table 3| Yearly incidence of any and referable diabetic retinopathy in participants using insulin treatment and without retinopathy at baseline

Time from last negative screen	Any retinopathy		Referable retinopathy	
	Annual incidence	Cumulative incidence	Annual incidence	Cumulative incidence
1 year	192.43 (177.70 to 206.50)	192.43 (177.70 to 206.50)	2.56 (1.13 to 4.70)	2.56 (1.13 to 4.70)
2 years	128.03 (120.00 to 136.85)	320.64 (304.86 to 334.53)	5.00 (3.33 to 6.50)	7.67 (4.78 to 10.71)
3 years	100.19 (92.02 to 109.50)	421.62 (403.10 to 437.67)	6.84 (4.23 to 9.43)	14.48 (9.68 to 18.66)
4 years	81.69 (74.32 to 89.49)	502.95 (482.26 to 525.51)	8.41 (4.40 to 12.90)	22.81 (15.20 to 30.30)

Data are incidence (95% confidence interval) per 1000 people. Incidence of background retinopathy is the difference between the incidences of any and referable retinopathy.

Table 4| Baseline characteristics of participants according to outcome

	No retinopathy (n=36 841)*	Any retinopathy (n=12 922)	P	Referable retinopathy (n=348)	P
Age (years)†	64.2 (11.3)	64.9 (11.3)	0.002	62.9 (11.3)	0.005
Known duration of diabetes mellitus (years)†	3.9 (4.2)	5.1 (4.9)	<0.001	5.6 (5.4)	<0.001
Age at diagnosis of diabetes mellitus (years)†	60.3 (11.3)	59.8 (11.5)	<0.001	57.3 (11.8)	<0.001
Sex‡					
Male	20 346 (55.5)	7183 (55.9)	0.232	195 (56.2)	0.786
Female	16 316 (44.5)	5659 (44.1)		152 (43.8)	
Treatment for diabetes mellitus‡					
Diet	13 918 (38.5)	3318 (26.0)	<0.001	72 (20.7)	<0.001
Oral hypoglycaemic agents	20 723 (57.3)	8326 (64.4)		234 (67.2)	
Insulin	1555 (4.3)	1114 (8.6)		42 (12.1)	

*Reference group. †Mean (standard deviation). ‡Number (%).

Table 5| **Parametric survival analysis with covariates in participants who developed diabetic retinopathy, according to grading category**

	Any retinopathy		Background retinopathy		Referable retinopathy	
Putative risk factor	**Crude hazard ratio (95% CI)**	**Adjusted hazard ratio (95% CI)**	**Crude hazard ratio (95% CI)**	**Adjusted hazard ratio (95% CI)**	**Crude hazard ratio (95% CI)**	**Adjusted hazard ratio (95% CI)**
Known duration of diabetes mellitus						
<5 years	1.00	1.00	1.00	1.00	1.00	1.00
5-9 years	1.39 (1.34 to 1.45)	1.29 (1.23 to 1.34)	1.39 (1.34 to 1.45)	1.29 (1.23 to 1.34)	1.54 (1.21 to 1.96)	1.35 (1.05 to 1.73)
≥10 years	1.92 (1.74 to 1.93)	1.68 (1.59 to 1.77)	1.82 (1.73 to 1.92)	1.67 (1.58 to 1.76)	1.99 (1.49 to 2.66)	1.61 (1.19 to 2.19)
Age at diagnosis						
30-49 years	1.00	1.00	1.00	1.00	1.00	1.00
50-59 years	0.93 (0.89 to 0.98)	0.97 (0.92 to 1.02)	0.94 (0.89 to 0.99)	0.97 (0.92 to 1.02)	0.71 (0.54 to 0.94)	0.75 (0.57 to 0.99)
60-69 years	0.90 (0.86 to 0.95)	0.99 (0.94 to 1.05)	0.91 (0.87 to 0.96)	1.00 (0.95 to 1.06)	0.50 (0.37 to 0.67)	0.57 (0.42 to 0.77)
≥70 years	0.98 (0.03 to 1.03)	1.20 (1.13 to 1.27)	0.98 (0.93 to 1.04)	1.20 (1.13 to 1.27)	0.64 (0.47 to 0.88)	0.83 (0.60 to 1.16)
Treatment for diabetes mellitus						
Diet	1.00	1.00	1.00	1.00	1.00	1.00
Oral hypoglycaemic agents	1.48 (1.43 to 1.55)	1.41 (1.36 to 1.47)	1.48 (1.43 to 1.55)	1.42 (1.36 to 1.48)	1.78 (1.36 to 2.32)	1.61 (1.22 to 2.12)
Insulin	2.35 (2.19 to 2.51)	2.03 (1.89 to 2.18)	2.34 (2.19 to 2.51)	2.03 (1.89 to 2.18)	3.39 (2.32 to 4.97)	2.60 (1.73 to 3.90)

All factors were significant at P<0.001.