

# Risk factors for having diabetic retinopathy at first screening in persons with type 1 diabetes diagnosed under 18 years of age

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## Abstract

**Objective:** To determine the risk factors for having diabetic retinopathy (DR) in children and young people (CYP) with type 1 diabetes (T1DM) at first screening.

**Methods:** Records from the Diabetes Eye Screening Wales (DESW) service for people in Wales, UK, with T1DM diagnosed under age 18 years were combined with other electronic health record (EHR) data in the Secure Anonymised Information Linkage (SAIL) Databank. Data close to the screening date were collected, and risk factors derived from multivariate, multinomial logistic regression modelling.

**Results:** Data from 4,172 persons, with median (Lower Quartile, Upper Quartile) age 16.3 (13.0, 22.3) years and duration of diabetes 6.6 (2.3, 12.3) years were analysed. 62.6% (n = 2,613) had no DR, 26.7% (n = 1,112) background DR and 10.7% (n = 447) had referable DR (RDR). No RDR was observed under 19 years of age. Factors associated with an increased risk of DR were diabetes duration, elevated HbA<sub>1c</sub> and diastolic blood pressure. People diagnosed with T1DM before age 12 years had an odds ratio of 1.23 for developing DR for each year they had diabetes, compared with an odds ratio of 1.34 for those diagnosed at age 12 years or older.

**Conclusions:** This study found that 37.4% of the study cohort had DR at first screening, the risk being greater the longer the duration of diabetes or higher the HbA<sub>1c</sub> and diastolic blood pressure. In addition, people diagnosed at 12 years of age or over were more likely to have DR with each additional year with diabetes.

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25

26 Running Head: Risk factors for retinopathy at first screening in T1DM

27

## Introduction

29 Visual impairment and blindness, as a consequence of diabetic retinopathy (DR), are amongst the most  
30 feared complications of diabetes. The incidence and prevalence of sight-threatening DR (STDR) has  
31 however been slowly decreasing over the last several decades despite the increase in the prevalence of  
32 diabetes (ref.1-7). It has been recently reported in England and Wales that DR is no longer the leading cause  
33 of blindness in the working age population (ref.8). Also in a retrospective analysis of newly recorded  
34 certifications of visual impairment in Wales during 2007-2015 sight loss was reduced by 50% (ref.9). These  
35 observations may reflect the cumulative impact of better management of diabetes, the introduction of  
36 screening programs, better management of risk factors and earlier and more effective ophthalmologic  
37 interventions.

38 Good glycaemic and blood pressure management are pivotal in both primary prevention and the prevention  
39 of progression of DR. The introduction of intensive insulin therapy to optimise glycaemic management in  
40 children has been observed to have a beneficial effect on DR in multiple studies (ref.10-12). In children aged  
41 13–17 years with type 1 diabetes (T1DM) the risk of developing DR was reduced by 53% (ref.10) while in  
42 children and young people (CYP) aged 12 to 20 years DR was also reduced by 12% to 52% (ref.11). The  
43 benefit of such intensive management in the adolescent years remains evident many years later (legacy  
44 effect) even when HbA<sub>1c</sub> values deteriorate, becoming similar to those undergoing conventional insulin  
45 therapy (ref.12). Currently, the treatment for STDR, which encompasses severe non-proliferative DR (pre-  
46 proliferative DR [PPDR] and proliferative DR (PDR), is primarily by laser photocoagulation and/or  
47 intravitreal injections of inhibitors of vascular endothelial growth factors (anti-VEGF). The relatively recent  
48 addition of anti-VEGF treatment has improved visual outcomes in those with PDR and/or clinically  
49 significant macular oedema (CSMO) (ref.13). Vitrectomy may also be required when these measures are  
50 considered inadequate. It is well accepted that DR remains asymptomatic until it reaches an advanced stage  
51 (STDR) and that the benefit from treatment is best achieved early. This is the basis for the introduction of  
52 screening for DR, which has been shown to be of clinical benefit but also cost-effective (ref.14). The  
53 detection of any DR should help to emphasise the need for improving glycaemic and blood pressure  
54 management, to prevent progression to STDR.

55 Previous studies have shown that approximately 0.3% of the Welsh population and 0.2% of CYP under 16  
56 years have T1DM (ref.15, 16). The prevalence of DR in children and young people (CYP) with diabetes is  
57 low and extremely rare prior to puberty (ref.17, 18). The prevalence of DR has been found in CYP with  
58 diabetes to range between 10.5% and 57.6% depending on the age, duration of diabetes, methods of detecting  
59 DR and the care setting (ref.18-30). The youngest ages at which DR and STDR have been recorded is 5 and  
60 15 years respectively, with the shortest duration of diabetes being 5 years and only five cases of STDR have  
61 been observed in children below the age of 18 years (ref.29, 31). However, these studies involved relatively  
62 small numbers and therefore there is a need to more clearly understand the epidemiology of DR and related  
63 risk factors in a population with T1DM diagnosed below the age of 18 years.

64 Systematic screening programmes for DR were introduced in the UK in 2003 with the recommendation to  
65 begin screening from the age of 12 years onwards (ref.32). However, the International Society for Paediatric  
66 and Adolescent Diabetes (ISPAD) recommends annual screening to begin earlier from the age of 10 years  
67 or at the onset of puberty, if this is earlier (ref.33). In Wales there exists a single national community based  
68 DR screening programme for all persons with diabetes aged 12 years and over using a standardised quality  
69 assured methodology for image capture and grading of diabetic retinopathy, the guidelines for which  
70 originated from the Airlie House classification and its modified version used in the Early Treatment Diabetic  
71 Retinopathy Study (ref.34, 35) which was simplified for the purpose of populations studies in the UK  
72 (ref.36). Grading involves a primary grader whose findings are checked by a secondary grader with  
73 differences resolved by a more senior tertiary grader to arrive at the final grading. Patients are referred to  
74 the hospital eye service if they have severe pre-proliferative DR, PDR and/or maculopathy for further  
75 assessment and treatment as required. This provided us with a unique opportunity to investigate the risk  
76 factors relating to DR in the population of children and young persons with T1DM diagnosed before the age  
77 of 18 years in Wales, at the time of their first screening event (ref.37).

## 78 **Methods**

79 The study database was derived from both primary care (Welsh Longitudinal General Practice dataset,  
80 WLGP) and the Diabetic Eye Screening Wales (DESW) dataset and held in the Secure Anonymised  
81 Information Linkage (SAIL) Databank (Swansea University). SAIL is a repository of routinely collected

82 electronic health record (EHR) data for people living in or receiving medical services in Wales (ref.38, 39).  
83 This study was reviewed by the independent Information Governance Review Panel (IGRP) of the SAIL  
84 Databank and approved under the ID: 0493. Ethical approval was not required since only anonymised data  
85 was used.

86

## 87 **Data preparation**

88 The study cohort consisted of people in Wales diagnosed with T1DM under the age of 18 years. The method  
89 used to identify persons with T1DM necessitated a recorded diagnosis of T1DM plus a prescription for  
90 insulin close to their earliest diagnosis date, or a hospital inpatient episode because of diabetic ketoacidosis,  
91 or a prescription for a medical device used in the management of T1DM (blood glucose and ketone  
92 monitoring equipment, for example, monitors and testing strips) on at least 5 occasions in the 12-months  
93 following diagnosis. In addition, the Brecon cohort, which is a national register of persons with T1DM  
94 diagnosed while living in Wales below the age of 15 years (ref.40) was also used to ensure the cohort was  
95 as complete as possible.

96 DESW aims to conduct DR screening annually in all persons with diabetes registered with a GP located in  
97 Wales that meet the eligibility criteria (most notably, persons must be 12 years or older). When a person  
98 attends screening, after testing visual acuity, two 45° retinal fundus photographs (one centred on the fovea,  
99 and one nasal view) are captured for each eye following mydriasis. Trained graders then assess the images  
100 for the presence of diabetic retinopathy, with images graded according to a standardised grading protocol  
101 (ref.37). The initial dataset consisted of the findings from the initial eye screening event which resulted in a  
102 successful assessment for at least one eye. In addition to the DR grading the current age, age at diagnosis of  
103 diabetes, duration of diabetes, gender and whether the person was referred to a hospital eye department were  
104 recorded. The following data from primary care GP or reference sources obtained within 6 months of the  
105 date of initial DR screening were also included in the dataset: HbA<sub>1c</sub>, systolic and diastolic blood pressure,  
106 serum cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, creatinine  
107 and Body Mass Index (BMI). Since this data was derived from the WLGP data, its availability depended on  
108 whether the test was performed by one of the 76% of general practices contributing data to the SAIL

109 Databank (ref.41). A variable indicating whether persons were diagnosed with T1DM before the age of 12  
110 years was also added to the data to enable modelling of interactions with duration of diabetes.

111 The DESW service commenced in 2003 attaining national coverage in 2007 with all data from both periods  
112 included in this study. The extract of the DESW data in the SAIL Databank used in this study ended at the  
113 end of January 2018.

114

## 115 **Statistical Methods**

116 Median and quartiles are reported as measured values are typically not normally distributed. A univariate analysis  
117 was conducted to investigate differences between the two groups for each individual variable. For continuous  
118 variables the Mann-Whitney U test was employed while categorical variables were investigated using Pearson's  
119  $\chi^2$  test. Secondly, multivariate models were constructed to compare a reference group consisting of people with  
120 no DR with two comparison groups: (i) people with evidence of any DR which was evaluated using binomial  
121 logistic regression and (ii) people with background diabetic retinopathy (BDR) or referable diabetic retinopathy  
122 (RDR, PPDR or worse) separately, which was evaluated using multinomial logistic regression.

123 Variables from the univariate analysis that were different between groups were used in the initial multivariate  
124 models and backwards stepwise logistic regression was performed until only those variables that differed  
125 significantly remained in the model. People diagnosed with T1DM before the age of 12 years are usually  
126 managed less intensively than those diagnosed after 12 years of age. Therefore, the model included a term that  
127 allowed for the interaction between the duration of diabetes and whether the person was diagnosed with T1DM  
128 under age 12 years or not. The logical variables indicating whether the person was diagnosed before the age of  
129 12 years were retained regardless of whether they differed between groups, in order to evaluate their interaction  
130 with the duration of diabetes. In each of the logistic regression models, Nagelkere's Pseudo  $R^2$  (denoted  $R^2_N$ )  
131 and the in-sample prediction accuracy,  $A$ , were used to evaluate the model's goodness of fit.

132

## Results

133 In Wales, during 2003 to 20018, 4495 people were diagnosed with T1DM under the age of 18 years and  
134 invited for DR screening from the age of 12 onwards. 305 (6.7%) did not attend screening and of the  
135 remaining 4190 people only 18 (0.4%) had ungradable images at their first screening event. The median age  
136 of the study cohort at the time of T1DM diagnosis was 10.6 years and at initial DR screening was 16.3 years  
137 with a median duration of diabetes of 6.6 years. The median HbA<sub>1c</sub> was 72.6 mmol/mol (8.8%) and blood  
138 pressure was 120/70 mmHg. (Table 1).

139

140 Of the 4,172 people with gradable images at their first screening event 62.6% (2,613) did not have any  
141 evidence of DR, 26.7% (1,112) had BDR and 10.7% (447) had RDR with 4.1% (173) having proliferative  
142 DR in one or both eyes (Figure 1). Those who presented with any DR at their first screening event had higher  
143 HbA<sub>1c</sub>, blood pressure, LDL, cholesterol, creatinine and a longer duration of diabetes and these differences  
144 were even greater in those who presented with a referable level of DR (Supplementary table 1).

145 People who had had diabetes for a longer time were more likely to have DR at first screening, with the  
146 proportion of the population with DR increasing with increasing duration of diabetes almost linearly up to  
147 approximately 17 years duration (Figure 2a). After 5, 10, 15 and 20 years of diabetes duration 11.0%, 38.6%,  
148 68.4% and 83.9% respectively had evidence of BDR. RDR was only observed in those people having had  
149 diabetes for at least 8 years, thereafter the proportion of people with RDR increased linearly (Figure 2a). We  
150 found, after 10, 15 and 20 years duration 4.6%, 27.9% and 53.6% of people had RDR respectively. None of  
151 the CYP had evidence of RDR before the age of 18 years (Figure 2b). We observed that 11.4% of 12 year  
152 olds at first screening had evidence of early DR, increasing to 31.9% for 18 year olds (Figure 2b). A smaller  
153 proportion of people aged under 12 years at diagnosis of T1DM had DR at first screening than people  
154 diagnosed at age 12 years or older when controlling for duration of diabetes (Figure 2c). Those people  
155 diagnosed with T1DM at or over the age of 12 years acquired an additional risk of developing DR for each  
156 year they had T1DM than people diagnosed under the age of 12 years (Table 2). This difference in the  
157 proportion of people with DR persisted until approximately 20 years duration of diabetes, when the  
158 proportion of people with DR in both groups became comparable (Figure 2c).

159 In a multivariate binomial logistic regression analysis, presenting at first screening with an elevated HbA<sub>1c</sub>  
160 (odds ratio [OR] 1.09) and duration of diabetes (OR 1.23 for people diagnosed under age 12 and 1.34 for  
161 people diagnosed at age 12 or older) carried an increased risk of having DR (Table 2a). In the multivariate,  
162 multinomial model increased HbA<sub>1c</sub>, diastolic blood pressure and duration of diabetes were observed to  
163 increase the risk of BDR and RDR, with duration of diabetes having the greatest effect (OR 1.22 for BDR  
164 and 1.29 for RDR in people diagnosed under 12 years, and 1.32 and 1.40 for BDR and RDR respectively in  
165 people diagnosed at 12 years or over, Table 2b). The accuracy of the bivariate model was slightly better than  
166 the multivariate model which is to be expected as classifying people into three groups is a more difficult  
167 problem than classifying them into two groups. The Nagelkerke R<sup>2</sup><sub>N</sub> indicates the multivariate model was a  
168 slightly better fit than the bivariate model, but both models fit the data well, having R<sup>2</sup><sub>N</sub> > 0.75.

## 169 **Discussion**

170 This study involved a large cohort (4172) of children and young people diagnosed with T1DM under the  
171 age of 18 years and investigated the proportion with DR and associated risk factors at their first DR screening  
172 event. In this cohort the presence of any DR was seen in 37.4% and 10.7% had RDR although no one was  
173 found with RDR under the age of 18 years. The fraction of people with BDR at first screening increased  
174 almost linearly with age, with approximately 31.8% having BDR at first screening at age 18. Although none  
175 of the cohort had RDR at their first screening before the age of 19 years there was a linear increase thereafter  
176 increasing to 30.1% at the age of 25 years at first screening. Increased diabetes duration, elevated HbA<sub>1c</sub>,  
177 and diastolic blood pressure conferred a higher risk of having any DR, BDR or RDR at first screening.

178 To our surprise our retinal graders recorded the presence of BDR in approximately 10% of our cohort within  
179 the first 2 years after diagnosis at variance with previous studies (ref.35, 42-44). This is difficult to explain  
180 but may in part reflect the high quality of retinal images acquired and the rigorous grading procedure at  
181 DESW and/or a prolonged asymptomatic period prior to the diagnosis of diabetes. Another contributing  
182 factor may be that many of the diagnoses of DR at this stage is acknowledged to rely on a small number of  
183 microaneurysms, or even a solitary one. Similarly, the DCCT study observed that 9.9% of people with type  
184 1 diabetes had evidence of diabetic retinopathy within the first 2 years since diagnosis, based on 7-field  
185 stereoscopic colour retinal photographs, increasing to 15% with the addition of fluorescein angiography  
186 (ref.45). Consistent with many other studies (ref.46-48), we demonstrated in our study that the longer the  
187 duration of diabetes the greater the risk of developing DR. The proportion with BDR at 5 and 10 years was



188 approximately 11.0% and 38.6% respectively, and whereas there was no RDR seen up to 8 years after  
189 diagnosis, at 10 and 20 years duration approximately 4.6% and 53.6% had developed RDR.

190 We also observed that a greater proportion of those diagnosed with T1DM after the age of 12 years had DR  
191 when compared to those diagnosed prior to 12 years for the same diabetes duration. The median time to DR  
192 in those diagnosed after the age of 12 years was 10 years in comparison to a median time of 12 years in  
193 those diagnosed before the age of 12 years. The adverse impact of puberty on the risk of progression of DR  
194 has been observed in many other populations (ref.42, 49, 50) although not in others (ref.51).

195 Our study also found that a higher HbA<sub>1c</sub> was a risk factor for DR at first screening which is in agreement  
196 with many previous studies performed in the UK (ref.5, 46), Europe (ref.47, 52) and the US (ref.48, 53).  
197 The finding that increased diastolic blood pressure specifically increases the risk of DR at first screening is  
198 also in agreement with previous work (ref.48). In CYP hypertension is relatively uncommon and the median  
199 blood pressures in groups that had no DR, BDR and RDR at first screening were all in the normal range for  
200 adults, in particular the median diastolic blood pressure was in the ideal range for all groups. We note  
201 defining hypertension in CYP is usually done with reference to percentiles taking age into account rather  
202 than using absolute cut-offs, but often people with blood pressure under 120/80 mmHg are classified as  
203 having normal blood pressure regardless of age. We observed that a modest increase in diastolic blood  
204 pressure causes a relatively large increase in risk of DR at first screening, even when the diastolic blood  
205 pressure is within the normal range.

206 Other risk factors for DR found in some previous studies were HbA<sub>1c</sub> variability, total cholesterol, HDL, age  
207 at diabetes diagnosis (ref.5, 52) and male gender (ref.47). However, in our study cohort we found total  
208 cholesterol, LDL, HDL, triglycerides and gender not to be associated with the occurrence of DR. It is  
209 difficult to compare our results with previous longitudinal studies due to differences in study population and  
210 design.

211 A limitation of this study was that persons having undertaken screening but did not have additional EHR  
212 data which included the putative risk factors of interest within six months of the screening which was  
213 required by the model and therefore were excluded from the cohort and subsequent analysis. Only if the  
214 measurement of HbA<sub>1c</sub> is available within 6-months of the screening date is the person included in the model.  
215 Adding more variables to the model compounds this difficulty, leading to quite small cohorts due to the

216 relatively high levels of missing data. The key factor that influences whether the data is missing or not is  
217 when the measurements were performed, and since these data are gathered at all times through the year the  
218 data can be considered to be missing at random and consequently will not affect the results of statistical  
219 modelling. This limitation would be common to all study designs that incorporate routine data. Furthermore,  
220 this study did not have access to data from the hospital based ophthalmological services to confirm the  
221 diagnoses of RDR. However, a great advantage of our study is that the cohort of persons with type 1 diabetes  
222 is much larger than has been reported in previous work and that the DESW adopts standardised practices  
223 and data collection methods, and has the ability to link to other EHR data via the SAIL Databank, which  
224 also covers all of Wales.

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232 This study makes use of anonymised data held in the SAIL Databank, which is part of the national e-health  
233 records research infrastructure for Wales. We would like to acknowledge all the data providers who make  
234 anonymised data available for research.

## 235 **Summary**

### 236 **What was known?**

- 237 • Longitudinal studies have investigated risk factors for diabetic retinopathy in various populations.
- 238 • Screening services have improved outcomes and reduced incidence of blindness in people with diabetes.

- 239
- People with type 1 diabetes tend to experience poorer outcomes than those with type 2 diabetes because
- 240 they often have more difficulty with glycaemic management.

241 **What this paper adds**

- 242
- In our cohort of people with type 1 diabetes 37.4% had diabetic retinopathy and 10.7% had referable
- 243 diabetic retinopathy at first screening.
- We found that diabetes duration, elevated HbA<sub>1c</sub>, and diastolic blood pressure increase the risk of having
- 244 any grade of retinopathy at first screening.
- People diagnosed with type 1 diabetes at or over the age of 12 years acquired a slightly larger additional
- 245 risk of DR for each year of diabetes than people diagnosed under the age of 12 years.
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- 247

248 **Ethics declarations**

249 **Conflict of interest**

250 The authors declare they have no conflicts of interest.

251

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384

385 Figure 1: Proportion of the population with no DR (62.6%), BDR (26.7%) or RDR (10.7%) at  
386 first screening and the proportion of people that have PPDR (2.9%), PDR (2.9%), maculopathy  
387 (2.1%), PPDR with maculopathy (1.6%) and PDR with maculopathy (1.2%) at first screening.

388

389 Figure 2: Fraction of persons diagnosed with BDR or RDR at first screening as a function of  
390 (a) diabetes duration, (b) age at screening and the fraction of people diagnosed aged less than  
391 12 and aged 12 or older with any DR as a function of diabetes duration (c).

392

393

Table 1: Demographic and laboratory test information on the cohort of people with T1DM at the time of first DR screening event.

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Table 2: Results from the (a) multivariate binomial logistic regression model (b) multivariate multinomial logistic regression model.

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398



Age range	0-6		6-12		12-18		Whole cohort	
Description	Count	Median (LQ, UQ)	Count	Median (LQ, UQ)	Count	Median (LQ, UQ)	Count	Median (LQ, UQ)
Total n	851 (100%)		1747 (100%)		1592 (100%)		4190 (100%)	
Female gender	425 (50%)		914 (52%)		631 (40%)		1971 (47.0%)	
Age at diagnosis (years)	851 (100%)	3.47 (2.2, 4.8)	1747 (100%)	9.5 (8.0, 10.8)	1592 (100%)	14.2 (13.0, 15.9)	4190 (100%)	10.6 (7.0, 13.4)
Age at screening (years)	851 (100%)	14.2 (12.3, 21.4)	1747 (100%)	14.1 (12.4, 20.6)	1592 (100%)	17.9 (15.2, 24.0)	4190 (100%)	16.3 (13.0, 22.3)
Diabetes duration (years)	851 (100%)	11.3 (8.9, 17.9)	1747 (100%)	5.6 (3.1, 11.4)	1586 (100%)	2.7 (0.8, 9.8)	4186 (99.9%)	6.6 (2.3, 12.3)
HbA1c (mmol / mol)	390 (46%)	74.0 (65.0, 86.8)	822 (47%)	73.7 (63.9, 87.7)	743 (47%)	70.4 (56.2, 84.6)	1957 (46.7%)	72.6 (61.7, 86.0)
HbA1c (%)	390 (46%)	8.9 (8.1, 10.1)	822 (47%)	8.9 (8.0, 10.2)	743 (47%)	8.6 (7.3, 9.9)	1957 (46.7%)	8.8 (7.8, 10.0)
Systolic pressure (mmHg)	383 (45%)	120.0 (110.0, 130.0)	814 (47%)	119.0 (110.0, 128.0)	931 (59%)	120.0 (110.0, 130.0)	2129 (50.8%)	120.0 (110.0, 130.0)
Diastolic pressure (mmHg)	383 (45%)	70.0 (62.0, 78.0)	814 (47%)	70.0 (63.0, 78.0)	931 (59%)	70.0 (65.0, 80.0)	2129 (50.8%)	70.0 (61.0, 79.0)
Cholesterol (mmol/l)	245 (29%)	4.5 (3.9, 5.1)	507 (29%)	4.4 (3.8, 5.1)	639 (40%)	4.3 (3.7, 5.0)	1392 (33.2%)	4.4 (3.8, 5.1)
LDL (mmol/l)	144 (17%)	2.5 (2.0, 3.0)	302 (17%)	2.3 (1.8, 2.9)	406 (26%)	2.3 (1.8, 2.9)	853 (20.4%)	2.3 (1.8, 2.9)
HDL (mmol/l)	162 (19%)	1.5 (1.3, 1.7)	334 (19%)	1.4 (1.2, 1.7)	438 (28%)	1.3 (1.1, 1.6)	935 (22.3%)	1.4 (1.2, 1.7)
Creatinine (µmol/l)	203 (24%)	76.0 (64.5, 89.0)	469 (27%)	73.0 (63.0, 85.0)	656 (41%)	74.0 (63.0, 86.0)	1330 (31.7%)	74 (63, 86)
BMI (kg/m <sup>2</sup> )	294 (35%)	23.8 (21.12, 27.2)	611 (35%)	23.4 (21.1, 26.7)	784 (49%)	24.0 (21.3, 27.0)	1691 (40.4%)	23.8 (21.1, 26.9)

400

(a)

Variable	OR (95% CI), No DR vs. Any DR
Diabetes duration (diagnosed < 12)	1.23 (1.20, 1.26)
Diabetes duration (diagnosed $\geq$ 12)	1.34 (1.30, 1.37)
HbA <sub>1c</sub> (per 10mmol/mol)	1.09 (1.04, 1.15)

401

 $R_N^2 = 0.764$ 

402

 $A = 0.827$ 

403

(b)

Variable	OR (95% CI), No DR vs. BDR	OR (95% CI), No DR vs. RDR
Diabetes duration (diagnosed < 12)	1.22 (1.19, 1.24)	1.29 (1.26, 1.33)
Diabetes duration (diagnosed $\geq$ 12)	1.32 (1.29, 1.36)	1.40 (1.36, 1.44)
HbA <sub>1c</sub> (per 10mmol/mol)	1.07 (1.02, 1.14)	1.19 (1.10, 1.29)
Diastolic pressure	1.02 (1.01, 1.04)	1.04 (1.02, 1.06)

404

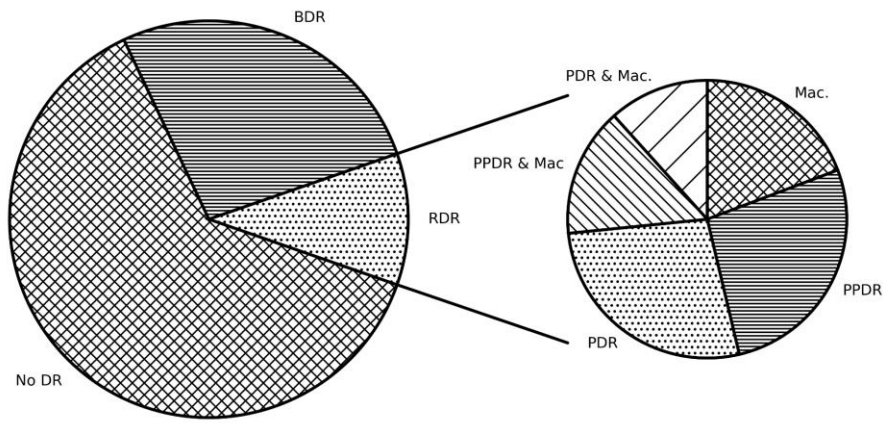
 $R_N^2 = 0.782$ 

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 $A = 0.721$ 

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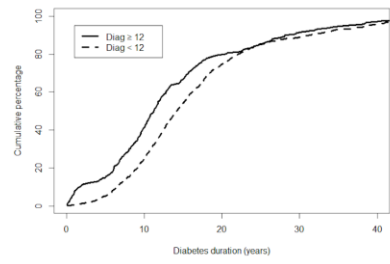
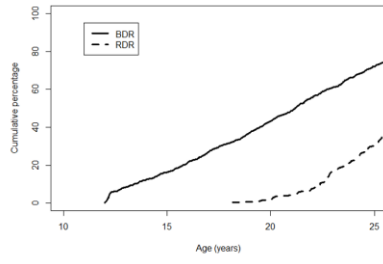
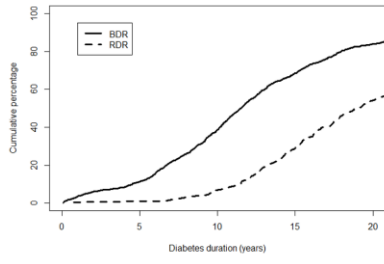
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