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ORIGINAL ARTICLE

Presence and development of diabetic retinopathy in 16 999 patients with type 1 diabetes in the Danish Registry of Diabetic Retinopathy

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Abstract

Purpose: To evaluate the five-year incidence of diabetic retinopathy (DR) and associated risk markers in patients with type 1 diabetes in the national Danish DR-screening programme.

Methods: Based on national data, we included all 16 999 patients with type 1 diabetes in the Danish Registry of Diabetic Retinopathy, who attended the national screening programme in the period 2013–2018. According to the worse eye at first screening, DR was classified (levels 0–4) and linked with various national health registries to retrieve information on diabetes duration, systemic comorbidity, and medication.

Results: At first screening, median age and duration of diabetes were 45.0 and 16.7 years, and 57.5% were males. The prevalence and five-year incidences for DR and progression to proliferative DR (PDR) were 44.2%, 8.9% and 2.0%, respectively. In multivariable Cox models, the incidence endpoints were associated with duration of diabetes (hazard ratio [HR] 1.76, 95% confidence interval [CI] 1.63–1.89, and HR 2.04, 95% CI 1.73–2.40 per 10 years), moderately low Charlson Comorbidity Index score (HR 1.27, 95% CI 1.10–1.47, and HR 2.80, 95% CI 2.23–3.51), and use of blood pressure lowering medication (HR 1.20, 95% CI 1.05–1.36, and HR 1.98, 95% CI 1.53–2.57).

Conclusion: In a study of all patients with type 1 diabetes from the Danish DR-screening programme, we identified duration of diabetes, systemic disease and use of anti-hypertensive treatment as consistent risk markers for incident and progressive DR.

KEYWORDS
diabetic retinopathy, incidence, prevalence, registry based, risk-factor, screening, type 1 diabetes

1 | INTRODUCTION

Diabetic retinopathy (DR) is the leading microvascular complication in type 1 diabetes (Grauslund et al., 2009; Klein et al., 2008), and regular eye screening is important to avoid irreversible vision loss (Stefansson et al., 2000). In Denmark, a national DR screening programme has been fully implemented since 2013, and along with the use of systemic diabetes care, this has resulted in a substantial 78% reduction in diabetes-related blindness (Blindbaek et al., 2021).

While type 2 diabetes accounts for the vast majority of patients with diabetes, it is recognized that the lifetime risk of DR is substantially higher in patients affected by type 1 diabetes. In a global study of 22 896 patients with diabetes, Yau et al. presented a considerably higher prevalence of any DR (77.3% vs. 25.2%) and proliferative DR (PDR) (32.4% vs. 3.0%) in patients with type 1 compared to type 2 diabetes (Yau et al., 2012). Likewise, in a Danish study of 17 152 patients with diabetes, the prevalence of DR for type 1 and 2 diabetes was 54.3% and 21.2% (Larsen et al., 2017).

To address the higher lifetime risk of DR in type 1 diabetes, prospective, population-based studies are important to identify potentially modifiable risk factors. In two independent 25-year prospective studies of patients with type 1 diabetes from Wisconsin and Denmark, Klein et al. (2008) and Grauslund et al. (2009) both reported a 42% risk of progression to PDR, but Klein et al. also reported that patients diagnosed most recently had a lower risk of PDR independently of other risk factors. While such studies have provided important data about DR in the past, contemporary studies are important to facilitate healthcare planning and identify present markers of risk or protection.

In the present study, we aimed to evaluate the prevalence and five-year risk of onset and progression of DR, as well as associated risk markers, in all patients with type 1 diabetes, who had attended screening during the first five years following establishment of the Danish national DR-screening programme.

2 | MATERIALS AND METHODS

2.1 | Study population

Since 2013, DR-screening has been nationally implemented in Denmark as a tax-funded initiative, which is freely available for all patients with diabetes (Andersen et al., 2016). Patients can attend screening at their local ophthalmic practice or a hospital-based screening facility. DR is classified according to the International Clinical Diabetic Retinopathy Disease Severity Scale, as proposed by Wilkinson et al. (2003) with increasing level of DR presented as levels 0 (no DR), 1–3 (mild, moderate and severe non-proliferative DR), and 4 (PDR present or previously treated with panretinal laser therapy). In 2018, national guidelines stated that gold-standard DR-screening should be performed as two-field or more mydriatic fundus photography (Grauslund et al., 2018), but this was, to some extent, already common practice beforehand.

It is mandatory for the screening facility to report screening results to the Danish Registry of Diabetic Retinopathy (DiaBase) (Andersen et al., 2016), which is a validated (Thykjaer et al., 2022) national clinical quality database that at the time of the study included 593 769 screening episodes of 207 200 patients diagnosed with either type 1 or type 2 diabetes, all of whom had attended DR-screening between January 2, 2013, and December 31, 2018.

In Denmark, DR grading is entirely performed by ophthalmologists, and we have previously found a 93% accuracy in DR-grading (Thykjaer et al., 2023). While there was a gradual shift from hospital-based screening to screening by practicing ophthalmologists during the study (Table 1), this was not expected to affect DR grading, as a high accuracy has been found for both groups (96% and 90%, respectively) (Thykjaer et al., 2023). Likewise, both groups adhere to the same national guidelines (Grauslund et al., 2018).

2.2 | National registers for disease classification and use of medicine

As identified in the DiaBase, we included data for all patients with type 1 diabetes from the Danish National Patient Registry (Schmidt et al., 2015), which includes International Classification of Disease version 10 (ICD-10) codes for diagnostic and procedural codes for hospital contacts (World Health Organization, 1992). This register was also used to calculate the Charlson Comorbidity Index score, which is an indicator of systemic disease (Brusselaers & Lagergren, 2017; Quan et al., 2011). For the Charlson Comorbidity Index score, we excluded diabetes, as this was present in all patients (Grauslund et al., 2021).

The Danish National Prescription Registry was used to provide data on redeemed prescriptions in accordance with the Anatomical Therapeutic Chemical (ATC) classification system (Pottegard et al., 2017), including insulin (A10A*), kidney protective and blood pressure lowering medicine (C03*, C07*, C08* and C09*), and lipid-lowering medicine (C10*).

The type of diabetes was classified using combined ICD-10 (E10*) and ATC (A10A*) codes indicating type 1 diabetes (Pedersen et al., 2022). Finally, we used the Danish Civil Registration System (Schmidt et al., 2014) to link data between registers and to obtain information regarding age and sex.

2.3 | Endpoint definition

According to the worse eye at the first DR-screening episode, prevalence of DR was defined as level 1–4 in any eye. For the longitudinal endpoints, we defined incident DR (no DR at the first examination followed by any DR [levels 1–4] at later examinations) and progression to PDR (no PDR [level 0–3] at first examination followed by PDR [level 4] at last examination). To improve the diagnostic accuracy, we only included those with both examinations performed at the same screening facility.

TABLE 1 Characteristics of patients with type 1 diabetes at their first occurrence in the Danish Registry of Diabetic Retinopathy according to level of diabetic retinopathy (DR) in the worse eye.

		Year of first screening						
	Overall	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	***p*-value**
Number of patients, *n*	16999	6056	4725	2834	1455	1116	813	
Sex, *n* (%) male	9774 (57.5)	3331 (55.0)	2744 (58.1)	1686 (59.5)	865 (59.5)	650 (58.2)	498 (61.3)	<0.001
Age, years (IQR)	45.0 (30.9–57.2)	45.3 (33.5–56.6)	46.5 (33.2–58.3)	44.2 (28.3–57.2)	41.5 (26.5–55.1)	43.1 (26.9–59.9)	42.4 (23.6–57.5)	<0.001
Duration of diabetes[a], years (IQR)	16.7 (7.4–20.4)	19.0 (10.8–19.8)	17.3 (8.2–20.6)	14.4 (6.1–21.3)	11.5 (2.6–21.9)	11.5 (2.0–22.9)	8.7 (1.1–21.5)	<0.001
Charlson Comorbidity Index score[b], *n* (%)								
0	12 542 (73.8)	4113 (67.9)	3490 (73.9)	2229 (78.7)	1164 (80.0)	888 (79.6)	658 (80.9)	<0.001
1	3418 (20.1)	1603 (26.5)	911 (19.3)	458 (16.2)	192 (13.2)	149 (13.4)	105 (12.9)	
2	700 (4.1)	214 (3.5)	232 (4.9)	102 (3.6)	68 (4.7)	47 (4.2)	37 (4.6)	
3 or more	339 (2.0)	126 (2.1)	92 (1.9)	45 (1.6)	31 (2.1)	32 (2.9)	13 (1.6)	
Use of medicine, *n* (%)								
Blood pressure lowering	6870 (40.4)	2674 (44.2)	1998 (42.3)	1031 (36.4)	475 (32.6)	416 (37.3)	276 (33.9)	<0.001
Cholesterol lowering	6856 (40.3)	2616 (43.2)	2008 (42.5)	1087 (38.4)	480 (33.0)	409 (36.6)	256 (31.5)	<0.001
Level of DR[c], *n* (%)								
0	9490 (55.8)	2637 (43.5)	2630 (55.7)	1852 (65.3)	997 (68.5)	785 (70.3)	589 (72.4)	<0.001
1	4571 (26.9)	2088 (34.5)	1291 (27.3)	617 (21.8)	269 (18.5)	190 (17.0)	116 (14.3)	
2	1132 (6.7)	527 (8.7)	290 (6.1)	122 (4.3)	86 (5.9)	56 (5.0)	51 (6.3)	
3	228 (1.3)	110 (1.8)	51 (1.1)	35 (1.2)	18 (1.2)	8 (0.7)	6 (0.7)	
4	1578 (9.3)	694 (11.5)	463 (9.8)	208 (7.3)	85 (5.8)	77 (6.9)	51 (6.3)	
Screening facility, *n* (%)								
Ophthalmic practice	5152 (30.3)	892 (14.7)	1580 (33.4)	1160 (40.9)	556 (38.2)	546 (48.9)	418 (51.4)	<0.001
Hospital	11 847 (69.7)	5164 (85.3)	3145 (66.6)	1674 (59.1)	899 (61.8)	570 (51.1)	395 (48.6)	

Note: Data are given as numbers (with percentages), median with interquartile ranges (IQR) or percentages.

[a]Duration of diabetes was only calculated for patients with at least one International Classification of Diseases version 10 code for diabetes or one Anatomical Therapeutic Chemical Classification code for treatment of diabetes.

[b]Charlson Comorbidity Index score (excluding diabetes) given by levels 0 (low), 1 (moderately low), 2 (moderately high) or 3 or more (high).

[c]Classification of DR given by the International Clinical Diabetic Retinopathy Severity Scale (Wilkinson et al., 2003).

2.4 | Statistical analyses

We present data as counts, median (with interquartile ranges [IQR]) or proportions. Differences between groups in Table 1 were tested by the k-sample test for equality of medians (continuous data) and chi-square tests (categorical data).

In Table 3, we used a multivariable logistic regression analysis to estimate the odds ratio (OR) of DR, and for the longitudinal analyses in Table 4, we performed a multivariable Cox regression analysis (which met the proportional hazard assumption) to estimate the hazard ratio (HR) of all three longitudinal endpoints. For all multivariable analyses, we adjusted for age, sex, levels of Charlson Comorbidity Index score (using no systemic comorbidity as comparator), use of blood pressure and lipid-lowering medicine, and we reported 95% confidence intervals (CI). It was not possible to include age at diabetes onset in the multivariable analyses, as there was a collinearity between this and age at index date. In Table 4, patients were included at the date of their first screening registered in DiaBase and followed until the earliest registration of an outcome, death, migration or end of follow up (December 31, 2018), whichever occurred first.

We used Stata 17.0 (StataCorp, College Station, Texas) for statistical analysis, and statistical significance was considered as p-values lower than 0.05 and 95% CIs that did not include 1.

2.5 | Permissions

The present study is part of the Ocular And Systemic complications In DR Study (OASIS) (Grauslund et al., 2020) and was performed according to the tenets of the Helsinki Declaration. We have obtained permissions from the Danish Data Protective Agency (18/16231), the Danish Health Authorities (FSEID-00003964) and the Danish Clinical Registries (DIABASE-2018-12-11). For register-based studies in Denmark, it is not required to obtain informed consent from patients or permission from the Danish National Committee on Health Research Ethics.

TABLE 2 Prevalence at baseline and development during follow-up of diabetic retinopathy (DR) in patients with type 1 diabetes in the Danish Registry of Diabetic Retinopathy.

	Baseline, *n* (%)	Follow-up, *n* (%)	
	Prevalence of DR[a]	Incidence of DR[b]	Progression to PDR[c]
Overall	7509 (44.2)	1514 (8.9)	348 (2.0)
Sex			
Female	3106 (43.0)	675 (16.4)	155 (2.4)
Male	4403 (45.0)	839 (15.6)	193 (2.2)
Age			
<30 years	985 (24.4)	473 (15.5)	53 (1.3)
30–59 years	4806 (50.6)	785 (16.7)	208 (2.5)
>60 years	1718 (49.6)	256 (14.7)	87 (2.9)
Duration of diabetes[d]			
<10 years	683 (12.5)	456 (9.5)	25 (0.5)
10–20 years	3379 (53.9)	672 (23.3)	166 (2.9)
>20 years	3440 (66.9)	379 (22.3)	157 (3.8)
Charlson Comorbidity Index score[e]			
0	4500 (35.9)	1240 (15.4)	168 (1.4)
1	2475 (72.4)	221 (23.4)	148 (5.6)
2	338 (48.3)	42 (11.6)	20 (3.6)
3	196 (57.8)	11 (7.7)	12 (4.6)
Use of medicine			
Blood pressure lowering	4111 (59.8)	508 (18.4)	207 (3.7)
Cholesterol lowering	3807 (55.5)	528 (17.3)	177 (3.0)
Screening facility			
Ophthalmic practice	1815 (35.2)	431 (12.9)	95 (2.1)
Hospital	5694 (48.1)	1083 (17.6)	253 (2.3)

Note: Data are given as numbers (with percentages calculated as the overall proportion to each group) according to level of DR at worse eye at the time of the first registration in the Danish Registry of Diabetic Retinopathy.

Abbreviation: PDR, proliferative diabetic retinopathy.

[a]Prevalence: DR level>0 at first registration.

[b]Incidence: Progression from DR level 0 to >0 from first to last registration.

[c]Progression to PDR given as progression from <4 to 4 from first to last registration.

[d]Duration of diabetes was only calculated for patients with at least one International Classification of Diseases version 10 code for diabetes or one Anatomical Therapeutic Chemical Classification code for treatment of diabetes.

[e]Charlson Comorbidity Index score (excluding diabetes) given by levels 0 (low), 1 (moderately low), 2 (moderately high) or 3 or more (high).

3 | RESULTS

Of 16 999 patients with type 1 diabetes attending the national Danish DR-screening programme in 2013–2018, median age and duration of diabetes (with interquartile ranges [IQR]) at the time of the first screening were 45.0 (30.9–57.2) and 16.7 (7.4–20.4) years, and 57.5% were male (Table 1). Charlson comorbidity score (excluding diabetes) was above 0 for 26.2% of the included persons, and blood pressure lowering treatment and lipid-lowering treatment was used for 40.4% and 40.3%, respectively. DR levels 0–4 at the time of the first screening were present in 55.8%, 26.9%, 6.7%, 1.3% and 9.3%, respectively. Over time, there was an increasing number of first-time attendees, who did not have DR in any eye (43.3% vs. 55.7% vs. 65.3% vs. 68.5% vs. 70.3% vs. 72.4% for 2013, 2014, 2015, 2016, 2017 and 2018, respectively) but a decreasing rate of patients in blood pressure (44.2% in 2013 and 33.9% in 2018) and lipid-lowering therapy (43.2% in 2013 and 31.5% in 2018).

The overall prevalence of DR at the time of the first screening was 44.2%, and five-year cumulative incidences of any DR and progression to PDR were 8.9% and 2.0% (Table 2). Higher levels of all endpoints were found in patients with longer duration of diabetes, moderately low systemic comorbidity (as compared to no systemic comorbidity), and an increased use of blood pressure and lipid-lowering therapy.

In a multivariable regression model (Table 3), the prevalence of DR independently associated with male sex (OR 1.14, 95% CI 1.06–1.22), lower age (OR 0.87, 95% CI 0.81–0.93 per 10 years), longer duration of diabetes (OR 3.22, 95% CI 3.07–3.39 per 10 years), systemic comorbidity (OR 3.36, 95% CI 3.06–3.68, OR 1.29, 95% CI 1.08–1.54, OR 1.89, 95% CI 1.47–2.42 for Charlson comorbidity scores 1–3, respectively) and use of blood pressure (OR 1.70, 95% CI 1.56–1.85) as well as cholesterol-lowering therapy (OR 1.15, 95% CI 1.05–1.25).

In the prospective models (Table 4), the five-year incidence of DR and progression to PDR were independently predicted by duration of diabetes (HR 1.76, 95% CI 1.63–1.89, and HR 2.04, 95% CI 1.73–2.40 per 10 years), moderately low Charlson Comorbidity Index score (HR 1.27, 95% CI 1.10–1.47, and HR 2.80, 95% CI 2.23–3.51) and use of blood pressure lowering medicine (HR 1.20, 95% CI 1.05–1.36, and HR 1.98, 95% CI 1.53–2.57). In addition, a moderately high (HR 2.39, 95% CI 1.49–3.83) and high (HR 3.11, 95% CI 1.72–5.62) Charlson Comorbidity Index score predicted risk to PDR, and increasing age associated with a lower risk of incident DR (HR 0.74, 95% CI 0.67–0.82). Sex and use of cholesterol-lowering therapy did not associate with the upcoming risk of onset or progression of DR in any model.

In the temporal analyses of patients attending first screening in 2013, 2014 and 2015 (Table 5), we found an increasing one- and three-year risk of incident DR (1-year risk: 1.90–3.81 and 3-year risk: 11.09–24.97 events per 1000 person-years), but a lower risk of progression to PDR (one-year risk: 6.20 to 2.69 and three-year risk: 7.51 to 3.96 events per 1000 person-years).

4 | DISCUSSION

In the present study of all patients with type 1 diabetes attending the first five years of the Danish national DR-screening programme, we report prevalence and five-year incidences of DR onset and progression to PDR of 44.2%, 8.9% and 2.0%, respectively, and we have identified duration of diabetes, systemic comorbidity, and use of blood pressure lowering therapy as common risk factors of all endpoints.

In a prior study of 153 238 patients with type 2 diabetes in the Danish DR-screening programme (Grauslund et al., 2023), similar rates were 8.8%, 3.8%, and 0.2%, which underlines that type 1 diabetes is still associated with a higher risk to have or develop DR. Interestingly, the use of lipid-lowering therapy was associated with a 13%–30% lower risk of upcoming or progressive DR in type 2 diabetes but did not correlate to any endpoints in the present study. A potential explanation for these differences would be the demographic differences between the cohorts, which includes a lower age (45.0 vs. 66.9 years) but a longer duration of diabetes (16.7 vs. 5.3 years) in the present study of patients with type 1 diabetes. In conclusion, these results all underscore that type 1 diabetes is a distinct disease, which associates with a higher risk of DR.

In a recent meta-analysis of European studies, Li et al. reported a pooled DR-prevalence of 54.4% in type 1

TABLE 3 Multivariable logistic regression model with odds ratio and 95% confidence interval of prevalent diabetic retinopathy in at least one eye according to baseline characteristics in patients with type 1 diabetes in the Danish Registry of Diabetic Retinopathy.

	Increment	Odds ratio (with 95% confidence interval)
Sex	Versus women	
Men		1.14 (1.06–1.22)[a]
Women		Reference
Age	Per 10 years	0.87 (0.81–0.93)[a]
Duration of diabetes[b]	Per 10 years	3.22 (3.07–3.39)[a]
Charlson Comorbidity Index score[c]	Versus level 0	
0		Reference
1		3.36 (3.06–3.68)[a]
2		1.29 (1.08–1.54)[a]
3 or more		1.89 (1.47–2.42)[a]
Use of medicine	Versus no use	
Blood pressure lowering		1.70 (1.56–1.85)[a]
Cholesterol lowering		1.15 (1.05–1.25)[a]

Note: Multivariable model adjusted for age, sex, Charlson Comorbidity Index score, use of blood pressure lowering and cholesterol lowering medicine.

[a]Statistically significant.

[b]Duration of diabetes was only calculated for patients with at least one International Classification of Diseases version 10 code for diabetes or one Anatomical Therapeutic Chemical Classification code for treatment of diabetes.

[c]Charlson Comorbidity Index score (excluding diabetes) given by levels 0 (low), 1 (moderately low), 2 (moderately high) or 3 or more (high).

TABLE 4 Multivariable Cox regression models with hazard ratio and 95% confidence interval of incident diabetic retinopathy (DR) and progression to proliferative DR in at least one eye according to baseline characteristics in patients with type 1 diabetes in the Danish Registry of Diabetic Retinopathy.

		Hazard ratio (with 95% confidence interval)	
	Increment	Incident DR[a]	Progression to PDR[b]
Sex	Versus women		
Men		1.07 (0.96–1.19)	0.95 (0.77–1.18)
Women		Reference	Reference
Age	Per 10 years	0.74 (0.67–0.82)[c]	0.84 (0.68–1.03)
Duration of diabetes[d]	Per 10 years	1.76 (1.63–1.89)[c]	2.04 (1.73–2.40)[c]
Charlson Comorbidity Index score[e]	Versus level 0		
0		Reference	Reference
1		1.27 (1.10–1.47)[c]	2.80 (2.23–3.51)[c]
2		1.03 (0.75–1.40)	2.39 (1.49–3.83)[c]
3 or more		0.96 (0.53–1.74)	3.11 (1.72–5.62)[c]
Use of medicine	Versus no use		
Blood pressure lowering		1.20 (1.05–1.36)[c]	1.98 (1.53–2.57)[c]
Cholesterol lowering		0.98 (0.86–1.12)	0.98 (0.76–1.25)

Note: Multivariable model adjusted for age, sex, Charlson Comorbidity Index score, use of blood pressure lowering and cholesterol lowering medicine.
Abbreviation: PDR, proliferative diabetic retinopathy.
[a]Incident DR: progression from DR level 0 to >0 from first to last registration.
[b]Progression to PDR given as progression from DR level <4 to 4 from first to last registration.
[c]Statistically significant.
[d]Duration of diabetes was only calculated for patients with at least one International Classification of Diseases version 10 code for diabetes or one Anatomical Therapeutic Chemical Classification code for treatment of diabetes.
[e]Charlson Comorbidity Index score (excluding diabetes) given by levels 0 (low), 1 (moderately low), 2 (moderately high) or 3 or more (high).

TABLE 5 Risk of incident diabetic retinopathy (DR) and progression to proliferative DR (PDR) in at least one eye within one and three years according to year of first screening registration in patients with type 1 diabetes in the Danish Registry of Diabetic Retinopathy.

		One year		Three years	
	Persons at risk (number)	Observations time (years)	Incidence rate (events per 1000 person-years)	Observations time (years)	Incidence rate (events per 1000 person-years)
Incident DR[a]					
2013	2637	2625.04	1.90	7659.98	11.09
2014	2630	2612.52	2.30	7488.26	17.23
2015	1852	1838.45	3.81	5045.91	24.97
Progression to PDR[b]					
2013	5362	5321.57	6.20	15 579.20	7.51
2014	4262	4223.61	5.21	12 244.62	4.98
2015	2626	2605.36	2.69	7317.98	3.96

Note: Risk of DR worsening according to year of first DR-screening.
[a]Incident DR: progression from DR level 0 to >0 from first to last registration.
[b]Progression to PDR given as progression from DR level <4 to 4 from first to last registration.

diabetes (Li et al., 2020), which compares fairly well with the 44.2% found in the present study. On the other hand, the prevalence of DR in type 1 diabetes in our study was much lower than the 77.3% presented by Yau et al. in a global meta-analysis in 2012 (Yau et al., 2012). This might reflect a better management of systemic diseases in recent years, and it aligns well with our observation that in just three years, we found a decreasing three-year incidence rate of progression to PDR from 7.51 to 3.96 events per 1000 person-years.

Interestingly, US-based population-based studies SEARCH and TODAY recently reported DR prevalences of 49%–56% of patients with young onset of type 1 and type 2 diabetes (Jensen et al., 2023; TODAY Study Group, 2021). Although patients in our study had a slightly longer duration of diabetes (16.7 years vs. 12.0–12.5 in SEARCH and TODAY), the DR prevalence in our study (44.2%) was still a bit lower than in the United States. This could reflect underlying socioeconomic or demographic differences between United States and Denmark but might also indicate variance in glycemic or blood pressure control between groups.

While our study was strengthened by the longitudinal design, the use of validated national databases with a considerable amount of screening episodes and the inclusion of all patients with type 1 diabetes attending DR-screening in

a national programme, it is also important to acknowledge limitations. First, we did not have access to blood glucose, blood pressure or lipid measurements. Second, we were not able to include diabetic macular edema as an endpoint, as this has not been validated in the Danish national registers. Third, as in all registry-based studies, results would reflect diagnostic coding that is potentially subject to some uncertainty. Furthermore, register-based data precludes the acquisition of information concerning potential influential confounding. These may encompass lifestyle factors like body mass index, physical activity level, alcohol consumption and smoking habits. It is essential to acknowledge the potential for unmeasured confounding when interpreting the results. Fourth, we have to address the potential self-selection bias due to the optional nature of attending the screening programme. This bias could affect the generalizability of our findings, as persons who choose to participate in the screening programme may differ from those who did not participate. However, our results are based on data from a tax-funded eye-screening programme that ensures equal access and promotes equal participation across all societal strata and, consequently, encompassing a broad range of DR cases among patients with type 1 diabetes attending the DR-screening programme. Finally, as some patients may only have attended the national DR screening programme once, the incidence endpoints might have been higher than reported in the present study, as DR development or worsening by definition would require at least two screening episodes.

In conclusion, we report of DR prevalence and five-year risks of DR development or progression in all 16 999 patients with type 1 diabetes attending the Danish national DR-screening programme. Duration of diabetes, systemic disease and use of blood pressure lowering therapy were all identified as common markers for present and upcoming disease. For upcoming studies, it would be important to provide long-term data and to include glycemic control, in order to tailor the national screening programme to reflect the contemporary risk of sight-threatening DR.

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