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ORIGINAL ARTICLE

Presence and development of diabetic retinopathy in 153 238 patients with type 2 diabetes in the Danish Registry of Diabetic Retinopathy

Jakob Grauslund[1,2,3] | **Frederik Nørregaard Pedersen**[1,2] | **Nis Andersen**[4] | **Jens Andresen**[4] | **Toke Bek**[5] | **Sebastian Dinesen**[1,2,3] | **Javad Hajari**[6] | **Steffen Heegaard**[6] | **Kurt Højlund**[2,3] | **Caroline Schmidt Laugesen**[7] | **Ryo Kawasaki**[2,8] | **Sören Möller**[9] | **Katja Christina Schielke**[10] | **Anne Suhr Thykjær**[1,2,3] | **Lonny Stokholm**[9]

[1]Department of Ophthalmology, Odense University Hospital, Odense, Denmark

[2]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[3]Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark

[4]Organization of Danish Practicing Ophthalmologists, Copenhagen, Denmark

[5]Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark

[6]Department of Ophthalmology, Rigshospitalet-Glostrup, Copenhagen, Denmark

[7]Department of Ophthalmology, Zealand University Hospital Roskilde, Roskilde, Denmark

[8]Department of Vision Informatics, University of Osaka, Osaka, Japan

[9]Research Unit OPEN, Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[10]Department of Ophthalmology, Aalborg University Hospital, Aalborg, Denmark

Correspondence
Jakob Grauslund, Department of Ophthalmology, Odense University Hospital, J. B. Winsløws Vej 4, DK-5000 Odense C, Denmark.
Email: jakob.grauslund@rsyd.dk

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Abstract

Purpose: The purpose of the study was to evaluate the prevalence and incidence of diabetic retinopathy (DR) along with associated markers in patients with type 2 diabetes in the Danish DR-screening programme.

Methods: We included all persons with type 2 diabetes in the Danish Registry of Diabetic Retinopathy, who had attended at least one episode of DR screening in 2013–2018. DR was classified as levels 0–4 indicating increasing severity. Data were linked with various national health registries to retrieve information on diabetes duration, marital status, comorbidity and systemic medication.

Results: Among 153 238 persons with type 2 diabetes, median age and duration of diabetes were 66.9 and 5.3 years and 56.4% were males. Prevalence and 5-year incidences of DR, 2-step-or-more progression of DR and progression to proliferative DR (PDR) were 8.8%, 3.8%, 0.7% and 0.2%, respectively. In multivariable models, leading markers of incident DR and progression to PDR were duration of diabetes (HR 1.98, 95% CI 1.87–2.09; HR 2.89, 95% CI 2.34–3.58 per 10 years of duration) and use of insulin (HR 1.88, 95% CI 1.76–2.01; HR 2.40, 95% CI 1.84–3.13), while the use of cholesterol-lowering medicine was a protecting marker (HR 0.87, 95% CI 0.81–0.93; HR 0.70, 95% CI 0.52–0.93). From 2013 to 2015, 3-year incidence rates of PDR decreased from 1.22 to 0.45 events per 1000 person-years.

Conclusion: Nationally, among Danish individuals with type 2 diabetes attending DR screening, we identified duration of diabetes and use of insulin as the most important predictor for the development of DR, while cholesterol-lowering medicine was a protective factor.

KEYWORDS
diabetic retinopathy, epidemiology, incidence, prevalence, registry based, risk factor, screening

1 | INTRODUCTION

Diabetic retinopathy (DR) is a frequent complication in type 2 diabetes (Klein et al., 1984; Kostev & Rathmann, 2013), and regular eye screening is necessary to detect sight-threatening DR prior to irreversible visual loss (Stefansson et al., 2000).

In 2012, Yao et al. presented a global DR prevalence of 25.2% based on 9666 patients with type 2 diabetes from various studies worldwide. Duration of diabetes was reported

as a leading marker of DR and proliferative DR (PDR), which were 2.45 and 9.79 times more frequent in patients with a duration of more than 20 years as compared to those, who had been diagnosed within 10 years. In a more recent meta-analysis of 59 population-based studies of predominantly type 2 diabetic patients, Teo et al. (2021) reported a 22.3% prevalence of DR. However, the type of diabetes was not explicitly identified in more than one-third of the studies, and neither included more than 2500 patients. From a Danish perspective, Hove et al. (2004) found higher numbers in 10 851 patients with type 2 diabetes, of which 31.5% had DR and 2.9% had been diagnosed with PDR.

Incidence studies on DR in non-hospital-based populations are uncommon in type 2 diabetes, and we are not aware of any studies including more than 757 persons (Sabanayagam et al., 2019). In a prospective, population-based study from Wisconsin, Klein et al. presented 10-year incidences of DR in 67%–79%, progression of DR in 53%–69% and progression to PDR in 10%–24% of patients with type 2 diabetes. However, these data were published in 1994, and they are no longer contemporary, given the advancements in glycaemic (UKPDS, 1998a, 1998b), blood pressure and cholesterol (UKPDS, 1998a, 1998b) control within the last decades (American Diabetes Association Professional Practice C et al., 2022a, 2022b).

The aim of the present study was to evaluate the current prevalence, incidences and associated risk factors of DR in all patients with type 2 diabetes, who have attended DR screening in Denmark between 2013 and 2018.

2 | MATERIALS AND METHODS

2.1 | Study population

Diabetic retinopathy screening is nationally implemented in Denmark as a free service to all patients with diabetes. It is performed according to national guidelines (Grauslund et al., 2018), with retinal two-field or more photographs and the stage of DR defined according to the International Clinical Diabetic Retinopathy Disease Severity Scale (Wilkinson et al., 2003) as levels 0 (no DR), 1–3 (mild, moderate and severe non-proliferative DR) or 4 (PDR). Patients can either attend DR screening at practising ophthalmologists or at hospital-based screening units.

The Danish Registry of Diabetic Retinopathy (DiaBase) is the national Danish quality database for DR screening, which is mandatory to use for all screening ophthalmologists (Andersen et al., 2016). In Denmark, screening for DR is a tax-funded service provided by practising ophthalmologists and hospital-based screening clinics. The vast majority of patients with uncomplicated type 2 diabetes attend screening at practising ophthalmologists, while some of those with complicated type 2 diabetes (who are attending diabetic care at endocrinology departments at hospitals) receive hospital-based screening. DiaBase was nationally implemented in 2013, and at the onset of this study it included 593 769 DR-screening episodes of 207 220 patients, who had attended DR-screening between 2 January 2013 and 31 December 2018. For the present study, we included all 153 238 patients with type 2 diabetes from this cohort.

The level of DR was given by the level in the worse eye at the first examination. Longitudinal endpoints were defined as incident DR (no DR at the first examination followed by any DR at later examinations), 2-step-or-more progression of DR (advancing at least two steps between first and last examination, e.g. from DR-level 1 to DR-level 3) and incident PDR (no PDR at first examination followed by PDR at last examination). To improve the diagnostic accuracy, we only included those with both examinations performed at the same screening facility.

2.2 | Additional national registers

We used the *Danish Civil Registration System* (Schmidt et al., 2014) to link data between DiaBase and other national registers using the Central Persons Registration number, which is a unique personal identifier given to all inhabitants in Denmark. The *Danish Civil Registration System* was also used to extract data on age, sex and marital status.

To indicate systemic disease, we used the *Danish National Patient Registry* (Schmidt et al., 2015), which contains International Classification of Disease (ICD) version ten codes (World Health 1992) for all hospital-based contacts during the study. This register was also used to calculate the Charlson Comorbidity Index score (Brusselaers & Lagergren 2017), which we modified by excluding diabetes, as this was present in all patients (Grauslund et al., 2021). Hence, a person without other systemic diseased than diabetes would be given an index score of 0.

Finally, we used the *Danish National Prescription Registry* to provide information regarding redeemed prescriptions, according to the Anatomical Therapeutic Chemical (ATC) classification system (Kildemoes et al., 2011). For the purpose of the present study, we extracted data regarding medical use at the time of the first screening episode with respect to groups and all underlying subgroups (indicated by asterisk) of insulin (A10A*), non-insulin glucose-lowering medicine (A10B*), blood pressure-lowering medicine (C03*, C07*, C08* and C09*) and lipid-lowering medicine (C10*).

In the present study, we included all patients with presumed type 2 diabetes, defined according to diagnostic and therapeutic codes, as previously described (Pedersen et al., 2022). In brief, type 2 diabetes was defined by combined ICD-10 codes for type 2 diabetes (E11*) and ACT-codes for insulin (A10A*) and non-insulin glucose-lowering medicine (A10B*). For the specific combination of E11*, A10A* and A10B*, we included the following as indicative of type 2 diabetes: Yes-No-No, No-No-Yes, Yes-Yes-No, Yes-No-Yes, No-Yes-Yes, Yes-Yes-Yes and No-No-No.

2.3 | Statistical analyses

Data are presented as numbers, median (with interquartile ranges [IQR]), or percentages (Tables 1 and 2).

TABLE 1 Characteristics of patients with type 2 diabetes at their first occurrence in the Danish Registry of Diabetic Retinopathy according to level of diabetic retinopathy (DR) at the worse eye

		Year of first screening						
	Overall	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	
Number of patients, *n*	**153238**	**18074**	**37876**	**35558**	**20181**	**21126**	**20423**	***p*-Value**
Sex, *n* (%) male	86496 (56.4)	10248 (56.7)	21049 (55.6)	19868 (55.9)	11627 (57.6)	11902 (56.3)	11802 (57.8)	<0.001
Age, years (IQR)	66.9 (58.0; 73.8)	66.5 (58.0; 73.3)	67.6 (59.3; 74.2)	67.6 (58.9; 74.1)	65.9 (56.5; 73.2)	66.4 (56.8; 73.8)	65.8 (56.6; 73.5)	<0.001
Duration of diabetes[a], years (IQR)	5.3 (2.1; 9.8)	5.6 (2.6; 10.1)	5.8 (2.9; 10.2)	5.7 (2.8; 10.0)	4.7 (1.1; 9.1)	4.9 (1.1; 9.4)	4.1 (0.9; 9.1)	<0.001
Marital status, *n* (%)								
Never married	19080 (12.5)	2087 (11.5)	4311 (11.4)	4096 (11.5)	2637 (13.1)	2965 (14.0)	2984 (14.6)	<0.001
Married	90894 (59.3)	10991 (60.8)	22874 (60.4)	21343 (60.0)	11838 (58.7)	12143 (57.5)	11705 (57.3)	
Widowed or divorced	43264 (28.2)	4996 (27.6)	10691 (28.2)	10119 (28.5)	5706 (28.3)	6018 (28.5)	5734 (28.1)	
Charlson Comorbidity Index score[b], *n* (%)								
0	118308 (77.2)	13419 (74.2)	29453 (77.8)	27766 (78.1)	15544 (77.0)	16377 (77.5)	15749 (77.1)	<0.001
1	15332 (10.0)	2378 (13.2)	3809 (10.1)	3357 (9.4)	1980 (9.8)	1938 (9.2)	1870 (9.2)	
2	13315 (8.7)	1507 (8.3)	3154 (8.3)	3027 (8.5)	1791 (8.9)	1903 (9.0)	1933 (9.5)	
3 or more	6283 (4.1)	770 (4.3)	1460 (3.9)	1408 (4.0)	866 (4.3)	908 (4.3)	871 (4.3)	
Use of medicine, *n* (%)								
Insulin	24160 (15.8)	3731 (20.6)	6302 (16.6)	5474 (15.4)	2948 (14.6)	3101 (14.7)	2604 (12.8)	<0.001
Non-insulin glucose lowering	132610 (86.5)	15477 (85.6)	32377 (85.5)	30628 (86.1)	17607 (87.2)	18510 (87.6)	18011 (88.2)	<0.001
Blood pressure lowering	119188 (77.8)	14525 (80.4)	30339 (80.1)	27997 (78.7)	15238 (75.5)	15985 (75.7)	15104 (74.0)	<0.001
Cholesterol lowering	118414 (77.3)	14448 (79.9)	30454 (80.4)	27604 (77.6)	15044 (74.5)	15873 (75.1)	14991 (73.4)	<0.001
Level of DR[c], *n* (%)								
0	139700 (91.2)	15403 (85.2)	34069 (89.9)	32913 (92.6)	18578 (92.1)	19636 (92.9)	19101 (93.5)	<0.001
1	9495 (6.2)	1774 (9.8)	2737 (7.2)	1875 (5.3)	1120 (5.5)	1055 (5.0)	934 (4.6)	
2	2682 (1.8)	591 (3.3)	730 (1.9)	515 (1.4)	312 (1.5)	286 (1.4)	248 (1.2)	
3	419 (0.3)	86 (0.5)	87 (0.2)	78 (0.2)	66 (0.3)	53 (0.3)	49 (0.2)	
4	942 (0.6)	220 (1.2)	253 (0.7)	177 (0.5)	105 (0.5)	96 (0.5)	91 (0.4)	
Screening facility, *n* (%)								
Practicing ophthalmologist	135194 (88.2)	13116 (72.6)	33426 (88.3)	32526 (91.5)	17766 (88.0)	19389 (91.8)	18971 (92.9)	<0.001
Hospital	18044 (11.8)	4958 (27.4)	4450 (11.7)	3032 (8.5)	2415 (12.0)	1737 (8.2)	1452 (7.1)	

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 ten code for diabetes or one Anatomical Therapeutic Chemical Classification codes for the treatment of diabetes. Data were not available in 315 patients.

[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).

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).

We used a multivariable logistic regression analysis for the cross-sectional analyses (Table 3) and a Cox regression model (which met the proportional hazard assumption) for longitudinal analyses (Table 4). For the multivariable analyses in Tables 3 and 4, we adjusted for all factors that were statistically significant in Table 1 (sex, age, duration of diabetes, marital status, Charlson Comorbidity Index score, insulin, non-insulin glucose-lowering medicine, blood pressure-lowering medicine, cholesterol-lowering medicine, level of DR and screening facility). For these tables, we present odds ratio (OR) and hazard ratios (HRs) with 95% confidence intervals (95% CI) for each of the four endpoints (prevalent DR, incident DR, 2-step-or-more progression of DR and progression to PDR). In the Cox regression model, 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 (31 December 2018), whichever occurred first.

We used Stata 17.0 (StataCorp, College Station, Texas) for statistical analysis, and statistical significance was defined for p-values less than 0.05 and for 95% CIs that did not include 1.0.

2.4 | Permissions

The present study is part of the Ocular And Systemic complications in DR Study (OASIS) (Grauslund et al., 2020), and it was performed according to the tenets of the Helsinki Declaration. Prior to the study, we obtained permissions from the Danish Data Protective Agency (18/16231), the Danish Health Authorities (FSEID-00003964) and the Danish Clinical Registries

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

		Baseline, *n* (%)	Follow-up, *n* (%)		
		Prevalence of DR[a]	Incidence of DR[b]	2-step or more progression of DR[c]	Progression to PDR[d]
Overall		13 538 (8.8)	5362 (3.8)	1046 (0.7)	291 (0.2)
Sex	Female	5048 (7.6)	2321 (3.8)	422 (0.6)	112 (0.2)
	Male	8490 (9.8)	3041 (3.9)	624 (0.7)	179 (0.2)
Age	<30 years	53 (6.8)	25 (3.4)	6 (0.8)	<5[e]
	30–59 years	4077 (9.1)	1602 (3.9)	389 (0.9)	>94[e]
	>60 years	9408 (8.7)	3735 (3.8)	651 (0.6)	192 (0.2)
Duration of diabetes[f]	<10 years	6062 (5.7)	3160 (3.1)	571 (0.5)	123 (0.1)
	10–20 years	6224 (19.8)	1862 (7.4)	406 (1.3)	139 (0.4)
	>20 years	937 (37.6)	149 (9.6)	43 (1.9)	26 (1.1)
Marital status	Never married	2006 (10.5)	680 (4.0)	167 (0.9)	42 (0.2)
	Married	7700 (8.5)	3158 (3.8)	602 (0.7)	179 (0.2)
	Widowed or divorced	3832 (8.9)	1524 (3.9)	277 (0.6)	70 (0.2)
Charlson Comorbidity Index score[g]	0	9113 (7.7)	4127 (3.8)	756 (0.6)	166 (0.1)
	1	2454 (16.0)	656 (5.1)	174 (1.2)	78 (0.5)
	2	1205 (9.0)	404 (3.3)	79 (0.6)	32 (0.2)
	3	766 (12.2)	175 (3.2)	37 (0.6)	15 (0.2)
Use of medicine	Insulin	5545 (23.0)	1564 (8.4)	407 (1.7)	147 (0.6)
	Non-insulin glucose lowering	12 162 (9.2)	4909 (4.1)	946 (0.7)	260 (0.2)
	Blood pressure lowering	11 343 (9.5)	4294 (4.0)	828 (0.7)	243 (0.2)
	Cholesterol lowering	10 635 (9.0)	4243 (3.9)	796 (0.7)	226 (0.2)
Screening facility	Practicing ophthalmologist	9201 (6.8)	4409 (3.5)	702 (0.5)	170 (0.1)
	Hospital	4337 (24.0)	953 (7.0)	344 (2.0)	121 (0.7)

Note: Data are given as numbers (with percentages) according to level of DR at worse eye at the time of the first registration in the Danish Registry of Diabetic Retinopathy. 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]2-or-more-step progression of DR from first to last registration.

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

[e]In order to anonymize data, exact numbers cannot be presented, if numbers are <5 (or can be calculated from related cells).

[f]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 codes for treatment of diabetes. Data were not available in 315 patients.

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

(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.

3 | RESULTS

We included all 153 238 patients with type 2 diabetes, who had attended the Danish DR-screening programme in the period 2013–2018 (Table 1). Median age and duration of diabetes (with IQR) were 66.9 (58.0–73.8) and 5.3 (2.1–9.8) years, and 56.4% were males. Most attendees were married (59.3%), and most had a Charlson Comorbidity Index score of 0 (77.2%). Rates of use of insulin, non-insulin glucose lowering drugs, blood pressure lowering therapy and cholesterol lowering therapy at the first screening episode were 15.8%, 86.5%, 77.8% and 77.3%, respectively. Most patients did not have any DR at their first screening (91.2%), while the remaining patients had DR-levels 1–4 (5.2%, 1.8%, 0.3% and 0.6%, respectively). Most patients attended DR screening at a practicing ophthalmologist (88.2%).

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 2 diabetes in the Danish Registry of Diabetic Retinopathy

	Increment	Odds ratio (with 95% confidence interval)
Sex	Versus women	
Men		1.30 (1.25; 1.36)[a]
Women		Reference
Age	Per 10 years	0.77 (0.74; 0.81)[a]
Duration of diabetes[b]	Per 10 years	3.07 (2.96; 3.18)[a]
Marital status	Versus married	
Never married		1.28 (1.20; 1.36)[a]
Married		Reference
Widowed or divorced		1.06 (1.02; 1.11)[a]
Charlson Comorbidity Index score[c]	Versus level 0	
0		Reference
1		1.64 (1.55; 1.72)[a]
2		1.07 (1.00; 1.14)
3 or more		1.28 (1.17; 1.39)[a]
Use of medicine	Versus no use	
Insulin		2.34 (2.24; 2.44)[a]
Non-insulin glucose lowering		1.15 (1.07; 1.24)[a]
Blood pressure lowering		1.19 (1.12; 1.26)[a]
Cholesterol lowering		0.84 (0.80; 0.89)[a]

Note: Multivariable model adjusted for age, sex, duration of diabetes, marital status, Charlson Comorbidity Index score and use of 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 codes for treatment of diabetes. Data were not available in 315 patients.

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

The lowest number of patients initiated screening in 2013 (n = 18 074), while the highest number had an onset in 2014 (n = 37 876). While there were not clinically relevant differences between the years according to most parameters, there were statistically significant and clinically relevant changes from 2013 to 2018 with respect to lower use of insulin (20.6%–12.8%), blood pressure lowering therapy (80.4%–74.0%) and cholesterol lowering therapy (79.9%–73.4%). Finally, there was a decline in the prevalence of DR from 2013 to 2018 (14.8% vs. 10.1% vs. 7.4% vs. 7.9% vs. 6.5%), and the rate of hospital-based DR-screening decreased from 27.4% in 2013 to 7.1% in 2018.

Prevalence and 5-year incidences of DR, 2-step-or-more progression of DR and progression to PDR were 8.8%, 3.8%, 0.7% and 0.2%, respectively (Table 2). The prevalence of DR, incidence of DR, 2-step-or-more progression of DR and progression to PDR were higher for those with long duration of diabetes, a moderately low Charlson Comorbidity Index score, insulin use and DR screening in a hospital-based facility.

In the multivariable regression model (Table 3), the prevalence of DR was associated with: male sex (OR 1.30, 95% CI 1.25–1.36), age (OR 0.77, 95% CI 0.74–0.81 per 10 years of age), duration of diabetes (OR 3.07, 95% CI 2.96–3.18 per 10 years), never being married (OR 1.28, 95% CI 1.20–1.36) or widowed/divorced (OR 1.06, 95% CI 1.02–1.11), Charlson Comorbidity Index score of 1 (OR 1.64, 95% CI 1.55–1.72) or 3 or more (OR 1.28, 95% CI 1.17–1.39), use of insulin (OR 2.34, 95% CI 2.24–2.44), use of non-insulin glucose-lowering medicine (OR 1.15, 95% CI 1.07–1.24), blood pressure-lowering medicine (OR 1.19, 95% CI 1.21–1.26) and inversely with the use of cholesterol-lowering therapy (OR 0.84, 95% CI 0.80–0.89).

In the prospective part of the study (Tables 4 and 5) evaluating incident DR, 2-step-or-more progression of DR and progression to PDR, younger age (HR 0.88, 95% CI 0.82–0.94; HR 0.68, 95% CI 0.59–0.78; HR 0.68, 95% CI 0.52–0.89 per 10 years of age), longer duration of diabetes (HR 1.98, 95% CI 1.87–2.09; HR 1.93, 95% CI 1.71–2.18; HR 2.89, 95% CI 2.34–3.58 per 10 years), moderately low Charlson Comorbidity Index score (HR 1.17, 95% CI 1.07–1.27; HR 1.36, 95% CI 1.41–1.61; HR 2.38, 95% CI 1.81–3.14) and use of insulin (HR 1.88, 95% CI 1.76–2.01; HR 2.09, 95% CI 1.81–2.42; HR 2.40, 95% CI 1.84–3.13) independently predicted all three outcomes, while cholesterol lowering therapy was identified as a marker of protection (HR 0.87, 95% CI 0.81–0.93; HR 0.74, 95% CI 0.63–0.86; HR 0.70, 95% CI 0.52–0.93).

For the temporal analyses, we studied patients with an onset of DR-screening in 2013, 2014 and 2015. These were followed for 224 667; 247 934 and 248 567 years to the potential endpoints of incident DR, 2-step-or-more progression of DR and progression to PDR, respectively. For all three endpoints, one-year incidences decreased from 2013 to 2015 (1.05–0.83, 0.57–0.06 and 0.91–0.29 events per 1000 person-years, respectively). For three-year incidences, the risk of incident DR increased from 2013 to 2015 (3.21–7.28 events per 1000 person-years),

TABLE 4 Multivariable Cox regression models[a] with hazard ratio and 95% confidence interval of incident diabetic retinopathy (DR), 2-or-more-step progression of DR and progression to proliferative DR in at least one eye according to baseline characteristics in patients with type 2 diabetes in the Danish Registry of Diabetic Retinopathy

		Hazard ratio (with 95% confidence interval)		
	Increment	Incident DR[b]	2-step or more progression of DR[c]	Progression to PDR[d]
Sex	Versus women			
Men		1.04 (0.98; 1.11)	1.15 (1.01; 1.32)[e]	1.16 (0.90; 1.48)
Women		Reference	Reference	Reference
Age	Per 10 years	0.88 (0.82; 0.94)[e]	0.68 (0.59; 0.78)[e]	0.68 (0.52; 0.89)[e]
Duration of diabetes[f]	Per 10 years	1.98 (1.87; 2.09)[e]	1.93 (1.71; 2.18)[e]	2.89 (2.34; 3.58)[e]
Marital status	Versus married			
Never married		1.12 (1.02; 1.22)[e]	1.28 (1.06; 1.54)[e]	1.17 (0.82; 1.66)
Married		Reference	Reference	Reference
Widowed or divorced		1.14 (1.07; 1.22)[e]	1.13 (0.97; 1.31)	0.88 (0.66; 1.18)
Charlson Comorbidity Index score[g]	Versus level 0			
0		Reference	Reference	Reference
1		1.17 (1.07; 1.27)[e]	1.36 (1.14; 1.61)[e]	2.38 (1.81; 3.14)[e]
2		0.98 (0.88; 1.09)	1.07 (0.85; 1.36)	1.82 (1.24; 2.66)[e]
3 or more		1.03 (0.88; 1.20)	1.09 (0.78; 1.54)	1.64 (0.94; 2.84)
Use of medicine	Versus no use			
Insulin		1.88 (1.76; 2.01)[e]	2.09 (1.81; 2.42)[e]	2.40 (1.84; 3.13)[e]
Non-insulin glucose lowering		1.44 (1.27; 1.62)[e]	1.11 (0.88; 1.41)	1.11 (0.74; 1.67)
Blood pressure lowering		0.98 (0.91; 1.06)	0.94 (0.79; 1.11)	1.11 (0.79; 1.56)
Cholesterol lowering		0.87 (0.81; 0.93)[e]	0.74 (0.63; 0.86)[e]	0.70 (0.52; 0.93)[e]

Abbreviation: PDR, proliferative diabetic retinopathy.

[a]Multivariable model adjusted for age, sex, type and duration of diabetes, marital status, Charlson Comorbidity Index score, and use of medicine.

[b]Incident DR: progression from DR-level 0 to >0 from first to last registration.

[c]2-or-more-step progression of DR from first to last registration.

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

[e]Statistically significant.

[f]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 codes for treatment of diabetes. Data were not available in 315 patients.

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

while the risk of incident PDR decreased from 1.22 to 0.45 events per 1000 person-years in the same period.

4 | DISCUSSION

With 153 238 patients followed for up to 5 years, this is to our knowledge the largest epidemiologic DR-study in type 2 diabetes. In the entire population of patients with type 2 diabetes attending DR screening in Denmark, we found a considerably lower prevalence, incidence and progression of DR compared with earlier reports (Sabanayagam et al., 2019; Li et al., 2020). Potential explanations for this might include that the recent years have led to better treatment and optimized risk factor control in diabetes, which might decrease the onset and progression of DR (Chew et al., 2010). It could also reflect that the vast majority of patients with type 2 diabetes in the present study had a more favourable risk profile compared with hospital-selected populations, who typically comprise most study populations.

It is well known that duration of diabetes is a strong risk factor for developing DR in type 2 diabetes (Klein et al., 1984, 1994; Yau et al., 2012). The cumulative effect of elevated blood glucose induces retinal microvascular dysfunction, and for the same reason, life-long DR screening is recommended in the Danish guidelines for DR screening (Grauslund et al., 2018).

In type 2 diabetes, insulin is often used for patients with poorly controlled disease despite optimal non-insulin glucose lowering therapy (Nathan et al., 2009). It this study, we identified use of insulin as a marker of present, incident and progressive DR. In the multivariable models, patients who used insulin were 2.3 times more likely to have DR, and they had a 1.9–2.4 times higher risk for DR-development or progression. In a recent study of newly diagnosed type 2 diabetes, patients who used insulin were 3.6 times as likely to develop PDR within 5 years (Gange et al., 2021).

We were encouraged by the observation that use of cholesterol-lowering medicine was associated with a lower presence of DR and also predicted a better outcome, including a 30% lower risk of developing PDR. This was also reported by Kang et al., who studied 37 894 patients with type 2 diabetes and reported a 14% and a 36% lower rate of incident DR and PDR, respectively. Potential explanations for these findings might include that cholesterol lowering treatment may lead to an

TABLE 5 Risk of incident diabetic retinopathy (DR), 2-or-more-step progression of DR and progression to proliferative DR (PDR) in at least one eye within 1 and 3 years according to year of first screening registration in patients with type 2 diabetes in the Danish Registry of Diabetic Retinopathy

		1 year		3 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	15 403	15 258	1.05	42 955	3.21
2014	34 069	33 713	0.86	93 545	3.91
2015	32 913	32 548	0.83	88 167	7.28
2 step or more progression of DR[b]					
2013	17 768	17 585	0.57	49 663	0.89
2014	37 536	37 107	0.24	103 315	0.81
2015	35 303	34 874	0.06	94 956	1.15
Progression to PDR[c]					
2013	17 854	17 664	0.91	49 857	1.22
2014	37 623	37 187	0.48	103 542	0.67
2015	35 381	34 941	0.29	95 168	0.45

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]2-or-more-step progression of DR from first to last registration.

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

improved endothelial function and a lower vascular endothelial growth factor mediated angiogenesis (Cheung et al., 2010).

We also evaluated some temporal trends in present and incident DR and PDR for patients who attended their first screening in 2013, 2014 and 2015, respectively. Surprisingly, we observed some conflicting trends between endpoints and between 1- and 3-year data. One- and three-year risks of progression to PDR both decreased 2.7–3.1-fold for patients screened in 2015, compared to those with first episode of screening in 2013. On the other hand, the one-year risk of incident DR decreased from 1.05 to 0.83 events per 1000 person-years in the period 2013–2015, but this was followed by a subsequent three-year increase from 3.21 to 7.28 events per 1000 person-years. In a DR-screening population from Gloucestershire, Scanlon et al. recently reported that from 2013 to 2016, the incidence of DR decreased, while the incidence of PDR was unaltered. The reason for these discrepancies are difficult to explain but might reflect that DiaBase was nationally initiated in 2013 and might have required a learning-curve for DR-reporting among the practicing and hospital-based ophthalmologists.

The present study was strengthened by the large-scale, prospective design and the use of several validated national health registries. Limitations should be acknowledged as well. First, we did not have access to HbA1c, blood pressure or cholesterol values. Hence, we used surrogate markers like use of insulin and blood pressure and lipid-lowering medicine. In an earlier sub study of 11 212 patients with type 2 diabetes from the present cohort (Larsen et al., 2017), HbA1c were higher (58 mmol/mol) for patients with PDR compared to patients without DR (50 mmol/mol). On the contrary, systolic and diastolic blood pressure only differed marginally (131–135 and 80–75 mmHg, respectively), and cholesterol was almost similar (serum cholesterol 4.2–4.2 mmoL/L, HDL: 1.2–1.1 mmoL/L, LDL 2.1–2.0 mmoL/L, triglyceride 1.7–1.6 mmoL/L). Second, the present study was performed in the early years after DiaBase was established as a national initiative. Hence, DR rates might not truly represent the entire nation in the earliest years of the database, as geographical variations might have been more prominent at that time (Bek 2020). Third, we did not include diabetic macular oedema (DME) in the study. While an evaluation of visual acuity and DME is a vital part of the Danish screening programme (Andersen et al., 2016), it is not consistently reported in DiaBase, given that data are reported from multiple sources using different computer software. Not all of these are capable of reporting DME according to the definition used in DiaBase, and, hence, DME has not been validated as an endpoint of DiaBase. Fourth, the duration of diabetes is always uncertain in type 2 diabetes, which may be present for some time before diagnosis or initiation of treatment. Fifth, type 2 was defined according to diagnostic and therapeutic codes from national registers. While this helped us identify a large number of patients with type 2 diabetes who were not in the hospital system, this approach might not be as sensitive as individual measurements of HbA1c and C-peptide.

In conclusion, in this nationwide study of patients with type 2 diabetes attending DR screening, the DR prevalence was lower than previously reported. Low age, long duration of diabetes and the use of insulin were identified as predictors of present, incident and progressive DR, while use of cholesterol lowering therapy was a protective marker of all endpoints. Upcoming studies of the OASIS project will be able to address long-term outcomes of DR, and how these are influenced by systemic diseases and intervention.

ORCID

Jakob Grauslund https://orcid.org/0000-0001-5019-0736
Nis Andersen https://orcid.org/0000-0002-1133-7456
Toke Bek https://orcid.org/0000-0002-0409-2534
Steffen Heegaard https://orcid.org/0000-0001-5906-7670
Anne Suhr Thykjær https://orcid.org/0000-0002-2621-4360

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