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ORIGINAL ARTICLE

Diabetic retinopathy as an independent marker of cardiovascular disease in type 1 diabetes: Results from a nationwide longitudinal matched case–cohort study

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

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

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

[3]Department of Clinical Research, Research Unit OPEN, University of Southern Denmark, 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]Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark

[8]Division of Public Health, Department of Social Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan

[9]Department of Ophthalmology, Zealand University Hospital Roskilde, Roskilde, 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: To investigate diabetic retinopathy (DR) as a potential marker of cardiovascular disease (CVD) in adults with type 1 diabetes attending the Danish DR-screening programme and non-diabetes adults.

Methods: In this registry-based matched case–cohort study, we identified 16 547 adults with type 1 diabetes, who were registered in the *Danish Registry of Diabetic Retinopathy (DiaBase)*. Each case was age- and sex-matched by five non-diabetes individuals ($n = 82\,399$), and odds ratios (ORs) and hazard ratios (HRs) were estimated for incident and upcoming CVD in multivariable models.

Results: Adults with type 1 diabetes (median age 44.5 years, 57.6% male) were more likely to have prevalent CVD (OR 1.29; 95% CI, 1.20–1.38) and to develop CVD within 5 years (HR 1.19; 95% CI, 1.08–1.30) as compared to non-diabetes control. However, adults without DR were less likely to develop CVD (HR 0.84; 95% CI, 0.72–0.97) compared to the reference population. For adults with type 1 diabetes, there was an increasing risk for incident CVD for increasing levels of DR (HR 1.33, 1.95, 1.71 and 2.39 for DR-levels 1–4, respectively). Patients with CVD at the time of the first screening had a higher risk to develop DR during follow-up (HR 1.23; 95% CI, 1.02–1.49).

Conclusion: In a nationwide matched case–cohort study adjusted for potential confounders, DR was identified as an independent marker of prevalent and incident CVD in type 1 diabetes with increasing risk demonstrated for higher levels of DR. Likewise, CVD also independently predicted the risk of incident DR.

KEYWORDS
cardiovascular disease, diabetic retinopathy, registry-based, screening, type 1 diabetes

1 | INTRODUCTION

Worldwide, 8.4 million people are affected by type 1 diabetes, and the prevalence is predicted to increase with 60%–107% by 2040 (Gregory et al., 2022). Diabetic retinopathy (DR) has a long-term prevalence of 97% in type 1 diabetes (Grauslund et al., 2009a, Klein et al., 2008) and is among the leading causes of blindness (Grauslund

et al., 2009b; Klein et al., 2010). Screening for DR is highly recommended to prevent vision-loss and blindness (Stefansson et al., 2000), and it has been successfully implemented in Denmark (Grauslund et al., 2018) and various other countries (Holt, 2016; Scanlon, 2017; Wang et al., 2017).

While DR affect the retinal microvaculature, CVD is a common macrovascular complication (Sabanayagam & Wong, 2019) and a major cause of mortality (Vergès, 2020). There is a growing body of evidence to suggest that the presence of DR is associated with CVD (Guo et al., 2016; Hsu et al., 2021; Klein et al., 2004; Sabanayagam & Wong, 2019), but existing studies have often been cross-sectional, focusing on type 2 diabetes, based on limited sample sizes, have had selected study populations, and have not been able to test any potential dose–response relations between increasing levels of DR and CVD.

As there is a lack of long-term studies to address this issue in large cohorts, the aim of this nationwide matched case–cohort study was to examine the cross-sectional and longitudinal association between DR and CVD among patients with type 1 diabetes. In addition, we examined whether the risk of CVD increased in response to increasing levels of DR, and we inversely examined, if CVD also acts as an independent risk factor for DR in type 1 diabetes.

2 | MATERIALS AND METHODS

2.1 | Study design

In this longitudinal registry-based matched case–cohort study, we used data from four national quality registers. Cases were identified in the *Danish Registry of Diabetic Retinopathy (DiaBase)* and linked with data from three other national registers as well as matched randomly with five references each.

DiaBase is a national Danish quality database for DR-screening which is mandatory to use for all ophthalmologists and hospital-departments for adults with diabetes attending the screening programme (Andersen et al., 2016). It includes all adults older than 18 years diagnosed with diabetes in Denmark, who have attended the DR-screening programme, which was nationally implemented in 2013. At the onset of the present study, DiaBase included 591 136 DR-screening episodes of 205 970 adults.

In Denmark, DR-screening is a tax-funded service offered for free to all persons with diabetes, who can be attended either by practicing ophthalmologists or at hospital-based screening units. The screening is performed predominantly by fundus photography according to national guidelines (Grauslund et al., 2018), with retinal two-field or more images 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 (proliferative DR). Standards for retinal cameras used have been specified in the national guidelines (Grauslund et al., 2018). Grading has previously been validated (Thykjaer et al., 2023) and was either performed locally by practicing ophthalmologists or at telemedicine-based regional reading centers. In Denmark, DR-screening in type 1 diabetes is recommended after 5 years of diabetes, and screening intervals are individualized according to level of DR and systemic control.

2.2 | Data source

The *Danish Civil Registration System* (Schmidt et al., 2014) was used to link data between the DiaBase and the other national registers by a unique personal identifier, the Central Personal Registration number, which is given to each inhabitant in Denmark at birth or immigration. We also used this register to obtain data concerning the age, sex and marital status.

To identify patients with CVD and systemic comorbidity, we used the *Danish National Patient Registry (DNPR)*, which includes ICD-10 codes (World Health, 1992) of all hospital contacts in Denmark since 1977 (Schmidt et al., 2015). The *Danish National Prescription Registry* was used to provide information regarding redeemed prescriptions since 1995 according to the Anatomical Therapeutic Chemical (ATC) classification system (Kildemoes et al., 2011). For this study, we had access to data from these registers spanning the period from 1995 to 2018.

2.3 | Study population

Combing data from the *DNPR* and the *Danish National Prescription Registry*, we determined diabetes type of the adults registered in DiaBase. In brief, by combining ICD-10 codes for diabetes (E10* or E11*) with ATC-codes of redeemed prescriptions of insulin (A10A*) and oral blood glucose-lowering drugs (A10B*), we identified the type of diabetes, which allowed us to include all adults with type 1 diabetes and exclude all persons with other types of diabetes. We used the exact same criteria to define the types of diabetes as previously described (Grauslund et al., 2021).

In the present study, we defined cases as adults with type 1 diabetes collected from the DiaBase between 2 January 2013, and 31 December 2018 ($n = 16\,547$, Figure 1). The index date was set as the date of the first screening registered in DiaBase. Each case was matched by year of birth and sex with five individuals, who were not registered in DiaBase and did not have a pre-existing ATC-code or diagnostic code for diabetes at index date ($n = 82\,399$), leading to a final case–reference ratio of 1:4.87. The references were assigned the index date of their matched cases. Our study population contained 98 946 people, and through the 5 years of observation, it included 372 617 person-years at-risk for cases and references combined.

CVD was defined as in Table S1 (main categories: myocardial infarction, arteriosclerotic heart disease, coronary artery bypass grafting surgery, heart failure, pulmonary hypertension, cardiac arrhythmias, aortic

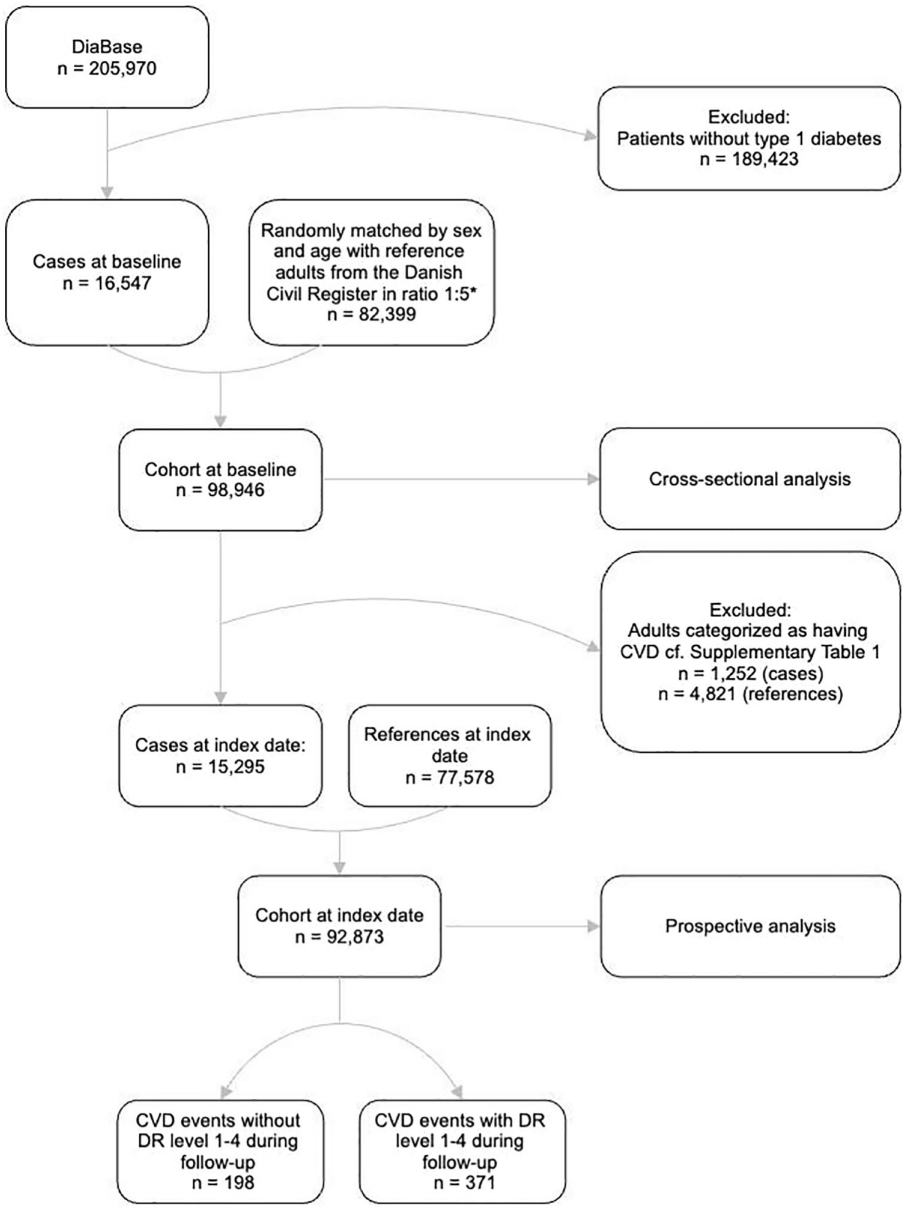

FIGURE 1 Flowchart showing the population progression in the study. *References were excluded if having diabetes by ICD and ATC codes, making the matched ratio 1:4.97. DR, diabetic retinopathy; ICD, International Classification of Disease and ATC, Anatomical Therapeutic Chemical Classification System.

diseases and vascular disease). The date for CVD was defined as the earliest recorded date, starting in 1995, when one of the designated diagnostic codes for CVD was registred in the *DNPR*.

First, we compared the prevalence of CVD at the beginning of the follow-up (at the index date) between adults with type 1 diabetes attending to the screening of DR and the references in the cross-sectional part of the study. Second, we excluded those patients with prevalent CVD in the beginning of the study and compared the incident CVD events between the adults with type 1 diabetes and their references. Third, we exclusively studied adults with type 1 diabetes without CVD at baseline. We compared patients with DR to those without DR in the beginning of the study and analysed the development of the CVD during the follow-up. Finally, we studied type 1 diabetic adults without DR at baseline, evaluating if those with CVD at baseline had a higher risk to develop DR during follow-up.

2.4 | Covariates and characteristics of groups

Diabetes duration was defined as the difference between the index date and the earliest registration of an ICD-code for diabetes or redeemed prescription of insulin or non-insulin glucose-lowering drugs, whichever came first.

We extracted data regarding medical use at index date concerning insulins (A10A*), non-insulin glucose-lowering drugs (A10B*), antihypertensive treatment (C03*, C07*, C08*, and C09*), and lipid lowering medicine (C10*). Systemic comorbidity was evaluated by a modified Charlson comorbidity index score that excluded diabetes, as it was present in all cases, and levels 0 through 3 indicating increasing severity of comorbidity. Other diseases of the Charlson comorbidity index score include chronic pulmonary disease, connective tissue disease and rheumatologic disease, ulcer disease, mild or moderate–severe liver disease, renal disease, hemiplegia

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).

		Level of DR[a]					
	Overall	**0**	**1**	**2**	**3**	**4**	***p*-Value**
Number of patients, *n*	16 547	9345	4431	1105	219	1447	
Sex, *n* (%) male	9529 (57.6)	5293 (56.6)	2524 (57.0)	715 (64.7)	149 (68.0)	848 (58.6)	<0.001
Age, years (IQR)	44.5 (30.5; 56.6)	41.2 (25.9; 54.8)	46.3 (35.0; 57.6)	47.0 (36.5; 57.7)	40.3 (32.2; 48.4)	51.7 (43.3; 61.0)	<0.001
Duration of diabetes, years (IQR)	16.3 (7.2; 20.4)	9.7 (3.6; 18.4)	19.5 (15.0; 21.0)	19.6 (16.2; 21.3)	19.5 (16.8; 20.7)	20.4 (19.5; 22.2)	<0.001
Charlson Comorbidity Index score, *n* (%)							<0.001
0 (low)	12 395 (74.9)	7985 (85.4)	3006 (67.8)	698 (63.2)	128 (58.4)	578 (39.9)	
1 (moderate low)	3260 (19.7)	914 (9.8)	1208 (27.3)	358 (32.4)	77 (35.2)	703 (48.6)	
2 (moderate high)	618 (3.7)	331 (3.5)	140 (3.2)	29 (2.6)	9 (4.1)	109 (7.5)	
3 or more (high)	274 (1.7)	115 (1.2)	77 (1.7)	20 (1.8)	5 (2.3)	57 (3.9)	
Use of medication, *n* (%)							
Insulin, *n* (%)	16 304 (98.5)	9140 (97.8)	4409 (99.5)	1099 (99.5)	218(99.5)	1438 (99.4)	<0.001
Glucose lowering treatment, excl. insulins, *n* (%)	1117 (6.8)	838 (9.0)	178 (4.0)	46 (4.2)	9 (4.1)	46 (3.2)	<0.001
Antihypertensive drugs, *n* (%)	6485 (39.2)	2644 (28.3)	2050 (46.3)	573 (51.9)	97 (44.3)	1121 (77.5)	<0.001
Cholesterol lowering drugs, *n* (%)	6494 (39.2)	2939 (31.4)	2005 (45.2)	537 (48.6)	83 (37.9)	930 (64.3)	<0.001
Cardiovascular disease, *n* (%)	1252 (7.6)	537 (5.7)	355 (8.0)	106 (9.6)	18 (8.2)	236 (16.3)	<0.001

Note: Data are given as numbers (with percentages) or median with interquartile ranges (IQRs).
[a]Classification of DR given by the International Clinical Diabetic Retinopathy Severity Scale.

or paraplegia, any malignancies (including leukaemia and lymphoma), and acquired immunodeficiency syndrome. The modification of the Charlson comorbidity index score is previously described in a study from 2021 (Grauslund et al., 2021).

For the non-diabetes reference group, CVD-categorization in Tables 2 and 3 is presented according to the level of DR for their matched controls.

2.5 | Statistical analyses

Descriptive data were reported as counts with proportions or medians with interquartile ranges. Differences in the characteristics between adults with type 1 diabetes and their matching referees were tested by the k-sample test for equality of medians (continuous data) and chi-square tests (categorical data) (Table 1 and Table S2). Present and level-specific DR at index date was used as a predictor, and prevalent and incident CVD was used as the outcome. The level of DR is given according to the level in the worse eye at the first screening episode in DiaBase. In the cross-sectional part of the study (Table 2), we estimated odds ratio (OR) with 95% confidence interval (CI) for CVD in crude, age- and sex-adjusted, and multivariable logistic regression models. In the longitudinal part of the study (Tables 3 and 4), we estimated hazard ratio (HR) for incident CVD in crude, age- and sex-adjusted, and multivariable Cox regression models. As references, we used the reference population in Tables 2 and 3, while in Table 4 the diabetes population without DR (level 0), was used as reference. In our reverse analysis, we used the proportion of the diabetes population with at least two screening episodes and no DR at index date to investigate whether the presence of CVD at index date predicted future development of DR. The proportional hazard assumptions were checked visually by log–log plots.

To perform the statistical analyses, we used Stata software version 17.0 (StataCorp, College Station, Texas, USA), and *p*-values less than 0.05 and 95% CIs that did not include 1.0 were considered statistically significant.

2.6 | Ethics and permissions

This study is part of the Ocular And Systemic complications In diabetic retinopathy Study (OASIS), initiated by the Danish Excellence Centre in Ophthalmic Epidemiology (DECODE-EYE) (Grauslund

TABLE 2 Odds ratios with 95% confidence intervals for CVD for patients diagnosed with diabetes type 1 and screened for diabetes retinopathy (DR) (cases) compared to age- and sex matched references according to the level of DR for cases at the first time of the first registration in the *Danish Registry of Diabetic Retinopathy*.

	Cases ($n=16547$)		References ($n=82399$)		Odds ratios (95% confidence intervals)		
Level of DR among cases	With CVD	Without CVD	With CVD	Without CVD	Crude model	Model adjusted for sex and age	Multivariable model[a]
Overall	1252	15295	4821	77578	1.32 (1.23; 1.41)	1.33 (1.25; 1.42)	1.29 (1.20; 1.38)
Level 0	537	8808	2496	43689	1.07 (0.97; 1.17)	1.07 (0.97; 1.18)	1.03 (0.93; 1.14)
Level 1–4 combined	715	6487	6487	33889	1.61 (1.47; 1.75)	1.63 (1.49; 1.79)	1.60 (1.46; 1.75)
Level 1	355	4076	1339	20723	1.35 (1.19; 1.52)	1.36 (1.20; 1.54)	1.35 (1.19; 1.53)
Level 2	106	999	326	5137	1.67 (1.33; 2.10)	1.69 (1.34; 2.13)	1.71 (1.35; 2.16)
Level 3	18	201	45	1065	2.12 (1.20; 3.74)	2.14 (1.21; 3.78)	2.00 (1.10; 3.64)
Level 4	236	1211	615	6964	2.21 (1.88; 2.59)	2.26 (1.92; 2.67)	2.19 (1.84; 2.60)

[a]Multivariable logistic regression model adjusted for sex, age and the modified Charlson comorbidity index (excluding diabetes) but including: chronic pulmonary disease, connective tissue disease and rheumatologic disease, ulcer disease, mild or moderate–severe liver disease, renal disease, hemiplegia or paraplegia, any malignancies (including leukaemia and lymphoma), and acquired immunodeficiency syndrome.

et al., 2020). The study was performed following the tenets of the Helsinki Declaration, with permissions obtained from the Danish Data Protective Agency (Journal number, 18/61231), the Danish Health Authorities (FSEID-00003964) and the Danish Clinical Registries (DIABASE-2018-12-11). According to Danish law, informed consent from patients or permission from the Danish National Committee on Health Research Ethics, is not required for registry-based studies.

3 | RESULTS

We identified 16547 adults with type 1 diabetes, who had attended the Danish DR-screening programme during the period 2013–2018 (Table 1). The median age was 44.5 years (interquartile range, 30.5–56.6 years), the median diabetes duration was 16.3 years (interquartile range, 7.2–20.4 years), 57.6% were men, and 7.6% were diagnosed with CVD at baseline. In general, persons with higher levels of DR were more likely to be older, have a higher Charlson comorbidity index score, and use antihypertensive and cholesterol lowering drugs. A higher prevalence of CVD was found for persons with a higher level of DR (8.0% vs. 9.6% vs. 8.2% vs. 16.3%; $p<0.001$) for DR-levels 1–4, respectively.

Among cases and references, CVD was diagnosed before the index date in 1252 (7.6%) and 4821 (5.8%) individuals, respectively (Table S2). Cases with CVD were older, had a longer duration of diabetes, were more likely to have systemic comorbidity, and had a higher level of DR than cases without CVD. While references with CVD were more probably male (65.1%) than those without CVD (57.0%), among adults with type 1 diabetes the proportion of male were similar in those with and without CVD ($p=0.91$).

When comparing with reference participants in a cross-sectional analysis, the presence of CVD was higher among cases at the time of the first DR-screening (multivariable adjusted OR 1.29; 95% CI, 1.20–1.38; Table 2), and with higher risk for increasing baseline levels of DR (multivariable adjusted OR 1.35 vs. 1.71 vs. 2.00 vs. 2.19 for DR-levels 1–4, respectively).

In a Cox regression analysis, a higher incidence of CVD was identified in cases as compared to references (Table 3). During the observation period, 569 of cases developed CVD during 61468 years of risk compared to 2383 references during 311149 years of risk, corresponding to an overall multivariable adjusted HR of 1.19 (95% CI 1.08–1.30). Compared to references, adults with any DR (levels 1–4 combined) had an increased risk to develop CVD (multivariable adjusted HR, 1.52; 95% CI, 1.35–1.71) in contrast to adults without DR (multivariable adjusted HR, 0.84; 95% CI, 0.72–0.97). Likewise, there was an increasing risk for incident CVD with incremental levels of DR (multivariable adjusted HR 1.25, 1.75, 1.53 and 2.17 for DR-levels 1–4, respectively).

When comparing cases with DR levels 1–4 to cases without DR at baseline, an increasing risk for incident CVD was found for increasing levels of DR (multivariable adjusted HR 1.33, 1.95, 1.71 and 2.39 for DR-levels 1–4, respectively; Table 4).

Among 9345 (56.6%) of the patients with type 1 diabetes and no DR in the beginning of the follow-up, there were 537 patients with prevalent CVD (5.7%) and 8808 (94.3%) without CVD. The risk of incident DR was higher among those with CVD than those without it (HR 1.23; 95% CI 1.02–1.49) in the multivariable analysis.

4 | DISCUSSION

In a national cohort of all adults with type 1 diabetes attending a DR-screening programme, we identified DR as an independent marker of present and 5-year incident CVD with an increasing risk for higher levels of DR. Inversely, those who had CVD also had a greater risk to develop DR in the upcoming 5 years.

Potential explanations for the dose–response relationship between DR and CVD may include factors as (i) shared pathogenic pathways (such as endothelial dysfunction and oxidative stress), (ii) DR signs reflecting generalized microvascular disease processes affecting multiple organ systems, and (iii) systemic microvascular disease igniting a cascade of inflammatory responses contributing to the formation of atherosclerotic heart disease (Sabanayagam & Wong, 2019).

TABLE 3 Hazard ratios with 95% confidence intervals for incident CVD after the index date[a] for type 1 diabetes patients with no prevalent CVD screened for DR and age- and sex-matched references according to level of DR.

	Cases ($n = 15\,295$)		References ($n = 77\,578$)		Hazard ratios (95% confidence intervals)		
Level of DR	Events of CVD[b]	Years of risk	Events of CVD	Years of risk	Crude model	Model adjusted for sex and age	Multivariable model[c]
Overall	569	61 468	2383	311 149	1.21 (1.10; 1.32)	1.21 (1.10; 1.33)	1.19 (1.08; 1.30)
Level 0	198	33 542	1116	164 761	0.87 (0.75; 1.01)	0.85 (0.73; 0.99)	0.84 (0.72; 0.97)
Level 1–4 combined	371	27 926	1267	146 388	1.53 (1.37; 1.72)	1.57 (1.39; 1.76)	1.52 (1.35; 1.71)
Level 1	177	17 773	723	90 025	1.24 (1.05; 1.46)	1.25 (1.06; 1.47)	1.25 (1.06; 1.47)
Level 2	63	4257	184	21 766	1.75 (1.32; 2.33)	1.79 (1.35; 2.39)	1.75 (1.31; 2.35)
Level 3	8	878	32	4669	1.33 (0.61; 2.88)	1.36 (0.63; 2.96)	1.53 (0.70; 3.34)
Level 4	123	5019	328	29 928	2.24 (1.82; 2.75)	2.30 (1.87; 2.83)	2.17 (1.74; 2.69)

Note: Results are shown for all patients and controls according to the level of DR at baseline.

[a]Index date defined as the date of the first registration in the *Danish Registry of Diabetic Retinopathy* for individuals with diabetes.

[b]Events of CVD given as the number of individuals with new registration of CVD after the index date.

[c]Multivariable logistic regression model adjusted for sex, age and the modified Charlson comorbidity index (excluding diabetes) but including: chronic pulmonary disease, connective tissue disease and rheumatologic disease, ulcer disease, mild or moderate–severe liver disease, renal disease, hemiplegia or paraplegia, any malignancies (including leukaemia and lymphoma), and acquired immunodeficiency syndrome.

TABLE 4 Hazard ratios with 95% confidence intervals for incident CVD after the index date[a] for type.

	Cases ($n = 15\,295$)		Hazard ratios (95% confidence intervals)		
Level of DR	Events of CVD[b]	Years of risk	Crude model	Model adjusted for sex and age	Multivariable model[c]
Level 0	198/8808	33 542	Reference	Reference	Reference
Level 1–4 combined	371/6487	27 926	2.23 (1.87; 2.65)	1.84 (1.55; 2.19)	1.63 (1.36; 1.94)
Level 1	177	17 773	1.66 (1.36; 2.03)	1.42 (1.16; 1.75)	1.33 (1.09; 1.64)
Level 2	63	4257	2.47 (1.86; 3.28)	2.07 (1.55; 2.75)	1.95 (1.46; 2.61)
Level 3	8	878	1.51 (0.75; 3.07)	1.77 (0.87; 3.60)	1.71 (0.83; 3.48)
Level 4	123	5019	4.12 (3.29; 5.16)	2.92 (2.33; 3.67)	2.39 (1.87; 3.06)

Note: One diabetes patient screened for DR according to the level of DR (level 0 used as reference).

[a]Index date defined as the date of the first registration in the *Danish Registry of Diabetic Retinopathy* for individuals with diabetes.

[b]Events of CVD given as the number of individuals with new registration of CVD after the index date.

[c]Multivariable logistic regression model adjusted for sex, age and the modified Charlson comorbidity index (excluding diabetes) but including: chronic pulmonary disease, connective tissue disease and rheumatologic disease, ulcer disease, mild or moderate–severe liver disease, renal disease, hemiplegia or paraplegia, any malignancies (including leukaemia and lymphoma), and acquired immunodeficiency syndrome.

To the best of our knowledge, there have been no other studies investigating all levels of DR according to risk of CVD. In a longitudinal study from Finland of 1683 patients with 30 or more years of 1 diabetes followed for 12 872 person-years, the absence of DR was a protective factor, while proliferative DR increased the risk of CVD with a factor 1.46 (Pongrac Barlovic et al., 2018). While the study was also based on a Caucasian population, comparisons are difficult given differences in sample size, observation time and generalizability.

In a nested case–control study from Brazil, Melo et al. found by multivariable logistic regression that patients with DR were more likely to develop CVD (OR 2.16; 95% CI, 1.16–4.02) compared to non-diabetic individuals (Melo et al., 2019). While the study design was very similar to the cross-sectional part of our study, differences might be due to different ethnicities and different sample sizes (57 cases in this Brazilian study vs. 16 547 cases in our study). In an ethnical comparable study of 996 type 1 diabetes patients from Wisconsin (Klein et al., 2004), the severity of DR was associated with angina and stroke (the 20-year cumulative incidences being 18.1% for angina and 5.9% for stroke). While this study was a population-based study of a large cohort, differences in diabetes care within the last 20 years would make further comparison between study results difficult.

Among the strengths of our study, we followed an entire national cohort of adults attending diabetic eye screening, with each case specifically age- and sex-matched by five individuals without diabetes. We had an observation-time of more than 300 000 years and were able to include patients across the entire spectrum of DR and add information of systemic comorbidity, antihypertensive and cholesterol lowering drugs. Finally, diagnostic coding of DR (Thykjaer et al., 2023) and CVD (Kümler et al., 2008; Rix et al., 2012; Sundbøll et al., 2016) have previously been validated.

Nevertheless, there are also some limitations, which are important to acknowledge. In a registry-based study, there will always be potential inaccuracies in coding practice and some factors will not be available or underreported in registers. Most importantly, we had no access to life style factors, BMI, smoking, HbA1c, LDL-cholesterol, albuminuria, and eGFR. Likewise, our

results would only apply to adults with type 1 diabetes attending the national DR-screening programme, though the attendance in Denmark is high (Thykjær et al., 2022).

In conclusion, results from this nationwide matched case–cohort study indicate DR as a useful marker of CVD in type 1 diabetes with increasing risk demonstrated for higher levels of DR. Likewise, CVD also independently predicted upcoming DR. As we have now demonstrated a longitudinal and dose–response connection between the severity of DR and upcoming risk of CVD in an entire national cohort, future studies might address, if early preventive intervention might alleviate the risk in high-risk patients and if results would also apply for persons with type 2 diabetes.

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ORCID

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
Jakob Grauslund https://orcid.org/0000-0001-5019-0736

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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