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ORIGINAL ARTICLE

Bidirectional 5-year risks of diabetic retinopathy, glaucoma and/or ocular hypertension: Results from a national screening programme

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Abstract

Purpose: We aimed to investigate if diabetic retinopathy (DR), glaucoma and/or ocular hypertension (OHT) are prospectively linked, as previous studies have proposed cross-sectional associations, but longitudinal data from larger cohorts are lacking.

Methods: We performed a bidirectional 5 years prospective, registry-based cohort study. We extracted data from national registers, including the Danish Registry of Diabetic Retinopathy, the Danish Civil Registration System, the Danish National Patient Register and the Danish National Prescription Registry. DR level was defined by the highest level of the two eyes. Glaucoma and/or OHT was defined by diagnostic codes (H40*) or at least three redeemed prescriptions of glaucoma medication (S01E*) within 1 year.

We included 205 970 persons with diabetes and 1 003 170 age- and gender-matched non-diabetes controls. Exposures were level-specific DR (i) and glaucoma and/or OHT (ii), and outcomes were hazard ratios (HRs) for 5 years incident glaucoma and/or OHT (i) and DR (ii).

Results: Persons with diabetes were more likely to develop glaucoma and/or OHT (multivariable adjusted HR 1.11, 95% CI 1.06–1.15), but this did not depend on the level of DR. In persons with diabetes, those with glaucoma and/or OHT were more likely to develop DR (multivariable adjusted HR 1.12, 95% CI 1.03–1.23) within 5 years.

Conclusion: In a national cohort, diabetes associated with a little higher risk of upcoming glaucoma and/or OHT, and, inversely, the presence of the latter predicted a higher risk of incident DR. Nevertheless, our data do not seem to justify including glaucoma evaluation in the national Danish DR-screening programme.

KEYWORDS
diabetes, diabetic retinopathy, epidemiology, glaucoma, ocular hypertension

1 | INTRODUCTION

Diabetes is a metabolic disorder. The number of people with diabetes globally is estimated at 415 million people, which is predicted to rise to 642 million by 2040 (Ogurtsova et al., 2017). Diabetes and its complications cause increased morbidity and mortality with diabetic retinopathy (DR) being the most frequent complication (Grauslund et al., 2009; Klein et al., 2008). Screening of DR reduces the risk of irreversible vision loss (Groeneveld et al., 2019; Stefánsson et al., 2000), and screening programmes have successfully been implemented in Denmark and elsewhere.

Glaucoma covers a range of diseases characterized by a progressive optic neuropathy and visual field defects. The number of people with glaucoma globally is estimated at 76 million people and is predicted to rise to 112 million by 2040 (Tham et al., 2014). Early diagnosis and treatment reduce the risk of irreversible vision loss (Leske et al., 2003). However, national glaucoma screening programmes have not been shown to be cost-effective (Burr et al., 2007; Moyer, 2013).

Meta-analyses have demonstrated an increased risk of glaucoma in patients with diabetes, but the included studies were primarily cross-sectional (Bonovas et al., 2004; Zhou et al., 2014). To our knowledge, only a few studies have assessed the association between DR and glaucoma (Apreutesei et al., 2014; Gangwani et al., 2016; Horwitz et al., 2016). In a cross-sectional study of 470 persons with DR, Gangwani et al. found no association between DR and glaucoma (Gangwani et al., 2016). In a retrospective study of eight persons with DR and glaucoma, Apreutesi et al. reported that persons with DR had a higher risk of glaucoma progression (Apreutesei et al., 2014). In a retrospective nationwide cohort study, Horwitz et al. found that patients with DR had a higher risk of glaucoma, but DR was only identified by ICD-10 codes, which excluded of the vast majority of persons with DR followed by practicing ophthalmologists (Horwitz et al., 2016).

While the pathogenesis of primary open-angle glaucoma has yet to be fully understood, increased intraocular pressure is a well-established risk factor (Leske et al., 2003). Impaired vascular supply to the optic nerve head has been suggested as a causative factor, and diabetes has been linked to both of these processes (Kanamori et al., 2004; Szaflik et al., 2010; Tham & Cheng, 2017). From a clinical perspective, it would be relevant to know whether DR, glaucoma and/or OHT predict each other in order to consider, whether screening for glaucoma and/or OHT should be included in DR screening, or if DR screening should be intensified in diabetes patients with glaucoma and/or OHT.

Based on longitudinal data from more than 1.2 million people, this study aimed to investigate if DR, glaucoma and/or OHT are longitudinally linked in a national cohort of patients screened for DR.

2 | METHODS

2.1 | The Danish health registries

The Danish Registry of Diabetic Retinopathy (DiaBase) is a national quality database containing data on all DR screenings of adult patients with diabetes since 2013 (Andersen et al., 2016). The screening is performed by practicing ophthalmologists or hospital departments, and results are reported to DiaBase. According to national guidelines, and based on the level of DR, flexible screening intervals are used, and screening is primarily based on retinal two-field or more mydriatic fundus images (Grauslund et al., 2018). Presence of DR is evaluated according to the International Clinical Retinopathy Disease Severity Scale: 0 (no DR), 1–3 (mild, moderate and severe non-proliferative DR) and 4 (proliferative DR) (Wilkinson et al., 2003).

The Danish National Patient Register contains information including the International Classification of Diseases (ICD) version 10 codes for all hospital contacts in Denmark (Schmidt et al., 2015).

The Danish National Prescription Registry contains information on all redeemed prescriptions at Danish community pharmacies, registered by the Anatomical Therapeutic Chemical Classification (ATC) System (Wallach Kildemoes et al., 2011).

The Danish Civil Registration System is a national register containing information regarding gender, marital status and vital status of persons with a civil registration number (Schmidt et al., 2014). A civil registration number is a unique personal identification number given to every Danish inhabitant, facilitating data linkage between the different national registers.

We extracted data from the described national registers. Of notice, health care services are free of cost for all Danish citizens, including the DR-screening programme.

2.2 | Study population

As cases, we included persons registered in DiaBase. Index date was defined as the date of the first registration in DiaBase. Level of DR was defined by the highest DR level of a patient's two eyes. To determine diabetes type, we combined ICD-10 codes for diabetes (E10* or E11*) and ATC-codes of redeemed prescriptions of insulin (A10A*) and oral blood glucose-lowering drugs (A10B*) (See Table S1). Diabetes duration was defined as the difference between the earliest registration of an ICD-code for diabetes or redeemed prescription of insulin or oral glucose-lowering drugs and the index date.

Each case was matched by gender and year of birth with five random controls selected from the Danish Civil Registration System, who were not registered in DiaBase. We excluded controls with diabetes, as defined by ICD-10 codes for diabetes or ATC-codes for redeemed prescriptions of insulin or oral blood glucose-lowering drugs. Hence, the final case–control ratio was 1:4.8. Controls were assigned the index date of their matched cases.

We retrieved data from DiaBase from 2013 to 2018, resulting in data from 205 970 cases and 1 003 170 matched non-diabetes controls.

In the prospective studies, we evaluated the risk of 5 years incident DR or glaucoma and/or OHT. We included data from the index date to incident outcome (DR, glaucoma or OHT), death, emigration or the end of study (31 December 2018), whichever came first. We excluded persons, who already had the outcome at the index date. In the prospective study evaluating glaucoma and/or OHT as a risk factor for incident DR, cases with

and without glaucoma and/or OHT were compared, and only cases with at least two registrations in DiaBase were included in order to examine the potential onset of DR. As a secondary outcome, we also evaluated the cross-sectional prevalent association between DR, glaucoma and/or OHT at the index date.

2.3 | Definitions

For this study, prevalent and incident glaucoma and/or OHT was defined by H40* ICD-10 codes given at an ophthalmology department or at least three redeemed prescriptions of glaucoma medication (S01E*) within 1 year. From redeemed prescriptions, date of diagnosis was determined by the first of the three. The majority of persons with glaucoma and/or OHT were included by redeemed prescriptions, since they are followed by practicing ophthalmologists. We did not extract data of glaucoma subtypes, since this was only possible for those with glaucoma and/or OHT who had hospital contact, and some subtypes (e.g. neovascular glaucoma) did not have specific ICD-10 codes.

Systemic comorbidities were evaluated in accordance with the updated Charlson comorbidity index score (Quan et al., 2011), after exclusion of diabetes-related codes, given that diabetes was only present in cases. By ATC-codes, we evaluated medication use of insulin (A10A*), oral blood glucose-lowering drugs (A10B*), antihypertensive treatment (C02*, C07*, C08*, C09*) and lipid lowering therapy (C10*).

2.4 | Statistics

Characteristics are presented as counts with proportions or medians with interquartile ranges. Differences between groups were tested using Chi-squared tests (χ^2) for categorical data and k-sample test of medians for continuous data (Tables 1,2).

In the prospective parts of the study, we estimated hazard ratios (HRs) with 95% confidence interval (CI) by Cox regression for incident glaucoma and/or OHT (Table 3) and incident DR (Table 4). In the cross-sectional study, level-specific DR at index date was the predictor and glaucoma and/or OHT the outcome, and we estimated odds ratios (ORs) with 95% CIs by logistic regression (Table S2). Results are given in crude, age- and gender-adjusted, as well as multivariable models adjusted for age, gender, marital status, use of antihypertensive drugs, cholesterol lowering drugs and Charlson comorbidity index. For references, we used the control population, albeit cases without glaucoma and/or OHT were used as reference in Table 4.

All analyses were performed using Stata 16.1 (StataCorp LP, College Station, TX, USA). *p*-values below 0.05 and 95% CIs not including 1.0 were considered statistically significant.

3 | RESULTS

For cases at index date, 56.6% were male, median age was 65.7 years and 74.4% had type 2 diabetes. Levels of DR were 83.4% (n = 171 795), 10.3% (n = 21 131), 3.2% (n = 6594), 0.6% (1162) and 2.6% (5288) for levels 0–4, respectively (Table 1).

At the index date, glaucoma and/or OHT was present in 4.7% (n = 9773) of cases and 3.3% (n = 32 763) of controls. For both cases and controls, those with glaucoma and/or OHT were more likely to be older, female, use antihypertensive drugs, use cholesterol lowering drugs and have a higher Charlson comorbidity index score. Furthermore, when comparing cases, those with glaucoma and/or OHT were more likely to have longer duration of diabetes and have higher levels of DR (Table 2).

After excluding all persons with glaucoma and/or OHT at index date, data were collected for a total of 658 843 person-years for cases (n = 196 197) and 3 216 921 person-years for controls (n = 970 407). During this period, 3639 and 13 125 events of glaucoma and/or OHT were registered for cases and controls, respectively (Table 3). Compared to controls, cases had an excess risk to develop glaucoma and/or OHT over 5 years in all models (multivariable adjusted HR 1.11, 95% CI 1.06–1.15), although we did not find statistically significant results for each DR level (Table 3). After excluding all cases with DR level 4 (due to potential neovascular glaucoma directly caused by DR), cases still had an increased risk to develop glaucoma and/or OHT over 5 years (multivariable adjusted HR 1.11, 95% CI 1.07–1.16, data not shown).

When observe ring only patients with diabetes but without DR, those with glaucoma and/or OHT at the index date had an increased risk of 5 years incident DR as compared to those without (538 events in 17 196 person-years vs. 12 817 events in 401 904 person-years, multivariable adjusted HR 1.12, 95% CI 1.03–1.23, Table 4). Furthermore, the former were more likely to develop DR level 4 (9.7% vs. 2.4%, Figure S1).

Compared to controls, cases were more likely to have glaucoma and/or OHT at the index date in the model including all individuals (multivariable adjusted OR 1.33, 95% CI 1.30–1.37), with the highest risk in those with higher DR levels (multivariable adjusted OR 1.20 vs. 1.53 vs. 1.36 vs. 2.69 vs. 6.11 for DR level 0–4, respectively. Table S2).

Persons with glaucoma and/or OHT at the index date were identified by redeemed prescriptions for 68.8% of cases and 64.9% of controls. Corresponding numbers for those identified after the index date were 86.0% of cases and 87.5% of controls (Table S3).

For persons with both diabetes and glaucoma and/or OHT, 69.0% were diagnosed with diabetes first, whereas 31.0% were diagnosed with glaucoma and/or OHT first. When comparing these two groups, the latter were more likely to have lower levels of DR (Table S4), and even had lower levels of DR compared to those without glaucoma and/or OHT at index date.

4 | DISCUSSION

In this registry-based national cohort study of 205 970 persons with diabetes and 1 003 170 non-diabetes controls, the former were independently 11% more likely to

TABLE 1 Characteristics of persons with diabetes at time of the first registration in the Danish registry of diabetic retinopathy according to level of diabetic retinopathy.

		Level of diabetic retinopathy					
	Overall	**Level 0**	**Level 1**	**Level 2**	**Level 3**	**Level 4**	***p*-value**
Number of patients, *n* (%)	205 970	171 795 (83.4)	21 131 (10.3)	6594 (3.2)	1162 (0.6)	5288 (2.6)	
Gender, % male	56.6	55.8	59.3	63.1	67.7	60.9	<0.001
Age, years (IQR)	65.7 (55.4–73.1)	66.2 (56.3–73.4)	63.5 (51.5–72.2)	62.0 (51.4–70.7)	55.9 (45.6–66.0)	61.3 (50.3–70.3)	<0.001
Type of diabetes, %							<0.001
Type 1	8.3	5.5	21.6	17.2	19.6	29.8	
Type 2	74.4	81.3	44.9	40.7	36.1	17.8	
Unknown	17.3	13.2	33.4	42.2	44.3	52.3	
Duration of diabetes, years (IQR)[a]							<0.001
Type 1	16.7 (7.4–20.4)	9.7 (3.6–18.7)	19.6 (15.1–21.0)	19.7 (16.4–21.3)	19.5 (16.8–20.7)	20.5 (19.5–22.2)	
Type 2	5.3 (2.1–9.8)	5.0 (1.9–9.1)	10.5 (5.3–15.4)	11.0 (5.4–15.8)	11.3 (5.4–15.8)	14.2 (8.9–19.0)	
Unknown	13.9 (8.4–19.2)	11.3 (6.4–16.3)	17.7 (13.2–20.0)	17.5 (12.9–20.0)	17.1 (13.0–19.7)	19.8 (18.1–21.2)	
Marital status, %							<0.001
Never married	15.0	14.3	17.9	18.9	24.4	20.3	
Married	57.7	58.1	55.9	55.1	50.6	54.4	
Widowed or divorced	27.3	27.6	26.2	26.0	25.0	25.3	
Charlson comorbidity index score, %							<0.001
0 (low)	72.2	75.6	60.2	53.9	49.6	34.9	
1 (moderate low)	13.5	10.6	23.7	28.7	33.3	41.4	
2 (moderate high)	9.1	9.0	8.8	9.3	9.8	13.3	
3 or more (high)	5.3	4.8	7.3	8.1	7.3	10.3	
Use of medication, %							
Insulin	33.2	25.2	68.1	75.5	78.9	88.0	<0.001
Glucose-lowering treatment, excl. insulins	75.4	79.4	59.0	60.6	57.2	34.5	<0.001
Antihypertensive drugs	74.9	74.5	75.1	76.9	74.1	86.0	<0.001
Cholesterol lowering drugs	73.9	74.3	71.4	71.2	67.1	75.0	<0.001
Glaucoma and/or ocular hypertension, %[b]	4.7	4.4	5.0	4.6	4.6	14.8	<0.001

Note: Data are given as numbers, medians 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]Glaucoma and ocular hypertension was defined as an H40* ICD-10 code given at an ophthalmology department or at least three redeemed prescriptions of glaucoma medication (S01E*) within 1 year of index date.

develop glaucoma and/or OHT within 5 years. Likewise, in persons with diabetes, those with glaucoma and/or OHT were independently 12% more likely to develop DR. Persons with diabetes were 33% more likely to have glaucoma and/or OHT with the highest prevalence in those with DR.

Previous studies have found a positive association between diabetes and glaucoma (Bonovas et al., 2004; Zhou et al., 2014) as well as DR and glaucoma (Apreutesei et al., 2014; Horwitz et al., 2016). The few studies examining association between DR and glaucoma were in general limited by low sample sizes (Apreutesei et al., 2014; Gangwani et al., 2016) and inclusion of persons with DR by ICD-10 codes only (Horwitz et al., 2016). In this study, we found that glaucoma and/or OHT were associated with a higher risk of incident DR. To our knowledge, no other studies have previously reported this.

DR level 0 was present in 92.4% of cases diagnosed with glaucoma and/or OHT before diabetes, compared to 70.2% of cases diagnosed with diabetes before glaucoma and/or OHT and 83.9% of cases without glaucoma and/or OHT. Our findings could represent intensive ophthalmologist examinations in persons with glaucoma and/or OHT and, hence, earlier diagnosis of diabetes compared to the average population. A study by Bek et al. has previously shown persons with screen-detected diabetes to have a lower prevalence of DR (Bek et al., 2009).

The strengths of the present study included the prospective design, in which more than 1.2 million persons were followed for more than 3.7 million person-years, that persons with diabetes were each matched with five random controls, that outcomes were defined in well-validated national registers and that we were able to adjust for multiple covariates. On the other hand,

TABLE 2 Differences between persons with diabetes (cases) and age- and gender-matched controls with and without glaucoma and/or ocular hypertension (OHT)[a] at time of the first registration in the Danish registry of diabetic retinopathy for cases.

	Case population			Control population		
Glaucoma and/or OHT	**Yes**	**No**	***p*-value**	**Yes**	**No**	***p*-value**
Number of patients, *n* (%)	9773 (4.7)	196 197 (95.3)		32 763 (3.3)	970 407 (96.7)	
Gender, % male	53.0	56.8	<0.001	51.5	56.7	<0.001
Age, years (IQR)	72.2 (65.1–78.6)	65.3 (55.0–72.8)	<0.001	74.5 (68.5–80.6)	65.2 (54.9–72.7)	<0.001
Type of diabetes, %			<0.001			N/A
Type 1 diabetes	6.0	8.4		N/A	N/A	
Type 2 diabetes	71.8	74.5		N/A	N/A	
Unknown	22.1	17.1		N/A	N/A	
Duration of diabetes, years (IQR)[b]			<0.001			N/A
Type 1 diabetes	20.4 (19.3–22.7)	16.2 (7.1–20.3)		N/A	N/A	
Type 2 diabetes	6.9 (3.1–11.9)	5.3 (2.0–9.6)		N/A	N/A	
Unknown	17.7 (11.8–20.3)	13.6 (8.1–19.0)		N/A	N/A	
Marital status, %			<0.001			<0.001
Never married	10.8	15.3		6.8	14.0	
Married	56.6	57.7		58.3	61.0	
Widowed or divorced	32.5	27.0		35.0	25.0	
Charlson comorbidity index score, %			<0.001			<0.001
0 (low)	65.3	72.6		79.2	86.4	
1 (moderate low)	17.0	13.2		6.8	4.5	
2 (moderate high)	10.9	9.0		10.2	6.9	
3 or more (high)	6.8	5.2		3.8	2.2	
Use of medication, (%)						
Insulin	36.2	32.9	<0.001	N/A	N/A	N/A
Glucose-lowering treatment, excl. insulins	72.8	75.6	<0.001	N/A	N/A	N/A
Antihypertensive drugs	83.9	74.3	<0.001	55.0	36.7	<0.001
Cholesterol lowering drugs	78.0	73.6	<0.001	34.1	22.9	<0.001
Level of DR, (%)			<0.001			N/A
Level 0	77.1	83.9		N/A	N/A	
Level 1	11.1	10.2		N/A	N/A	
Level 2	3.4	3.2		N/A	N/A	
Level 3	0.7	0.6		N/A	N/A	
Level 4	7.8	2.2		N/A	N/A	

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

[a]Glaucoma and/or OHT was defined as an H40* ICD-10 code given at an ophthalmology department or at least three redeemed prescriptions of glaucoma medication (S01E*) within 1 year of index date.

[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. DR: diabetic retinopathy.

limitations are important to consider. First, we were not able to adjust for glycaemic control or blood pressure. Second, there may be potential inaccuracies in data registration in national registers. Third, we were not able to distinguish between different types of glaucoma and/or OHT. Fourth, persons diagnosed with diabetes are recommended regular ophthalmologist examinations, which probably increase the chance of concurrent glaucoma and/or OHT being diagnosed and vice versa. It was not possible to adjust for this, as the number of visits at practicing ophthalmologists are not available in the registers for persons not attending DR-screening.

In conclusion, this national cohort study shows that persons with diabetes were 11% more likely to develop glaucoma and/or OHT, and those with glaucoma and/or OHT were 12% more likely to develop DR. We cannot say whether the association can be explained by shared pathophysiological pathways or draw any conclusions about whether persons with diabetes, glaucoma and/or OHT receive intensified screening and care. Although the present data do not seem to justify including glaucoma evaluation in the national Danish DR-screening programme, the introduction of artificial intelligence and potential of digital solutions in

TABLE 3 Hazard ratio (HR) with 95% confidence interval (CI) for incident glaucoma and/or ocular hypertension (OHT)[a] after index date[b] for persons screened for diabetic retinopathy (DR) (cases) compared to age- and gender-matched controls according to level of DR at the index date for cases.

Level of DR	Cases		Controls		HR (95% CI)		
	Events of glaucoma and/or OHT	Person-years, (n = 196 197)	Events of glaucoma and/or OHT	Person-years, (n = 970 407)	Crude model	Model adjusted for age and gender	Multivariable model[c]
All	3639	658 843	13 125	3 216 921	1.07 (1.03–1.11)[d]	1.12 (1.08–1.16)[d]	1.11 (1.06–1.15)[d]
0	2758	531 705	10 920	2 581 477	1.13 (1.08–1.17)[d]	1.15 (1.11–1.20)[d]	0.98 (0.94–1.02)
1	425	78 565	1373	387 653	0.98 (0.88–1.09)	1.03 (0.92–1.15)	1.03 (0.91–1.18)
2	159	24 405	431	122 378	0.98 (0.82–1.18)	1.09 (0.90–1.32)	1.08 (0.85–1.37)
3	38	4193	60	21 516	1.38 (0.91–2.09)	1.41 (0.92–2.16)	1.21 (0.68–2.16)
4	259	19 975	341	103 896	1.08 (0.92–1.27)	1.26 (1.06–1.51)[d]	1.10 (0.85–1.43)

[a]Glaucoma and/or OHT was defined as an H40* ICD-10 code given at an ophthalmology department or at least three redeemed prescriptions of glaucoma medication (S01E*) within 1 year of index date.

[b]Index date was defined as the time of the first registration in the Danish Registry of Diabetic Retinopathy for cases.

[c]Multivariable Cox regression model adjusted for age, gender, marital status, use of antihypertensive drugs, cholesterol lowering drugs and Charlson comorbidity index (myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease and rheumatologic disease, ulcer disease, mild or moderate–severe liver disease, hemiplegia or paraplegia, any malignancies (including leukaemia and lymphoma), acquired immunodeficiency syndrome, peripheral vascular disease, moderate or severe renal disease).

[d]Statistically significant.

TABLE 4 Hazard ratio (HR) with 95% confidence interval (CI) to develop diabetic retinopathy (DR) after the index date[a] for persons screened for diabetic retinopathy (DR) (cases) with and without glaucoma and/or ocular hypertension (OHT)[b] at index date.

	Cases with glaucoma and/or OHT		**Cases without glaucoma and/or OHT**		**HR (95% CI)**		
	Events of DR	**Person-years, (n = 5081)**	**Events of DR**	**Person-years, (n = 114 838)**	**Crude model**	**Model adjusted for age and gender**	**Multivariable model[c]**
Incident DR	538	17 196	12 817	401 904	1.19 (1.09–1.29)[d]	1.14 (1.04–1.24)[d]	1.12 (1.03–1.23)[d]

[a]Index date defined as the time of the first registration in the Danish Registry of Diabetic Retinopathy.

[b]Glaucoma and/or OHT was defined as an H40* ICD-10 code given at an ophthalmology department or at least three redeemed prescriptions of glaucoma medication (S01E*) within 1 year of index date.

[c]Multivariable Cox regression model adjusted for age, gender, marital status, use of antihypertensive drugs, cholesterol lowering drugs and Charlson comorbidity index (myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease and rheumatologic disease, ulcer disease, mild or moderate–severe liver disease, hemiplegia or paraplegia, any malignancies (including leukaemia and lymphoma), acquired immunodeficiency syndrome, peripheral vascular disease, moderate or severe renal disease).

[d]Statistically significant.

ophthalmology could change this conclusion in the near future.

AUTHOR CONTRIBUTIONS

Sperling, Stokholm, Thykjær, Pedersen, Möller, Laugesen, Andersen, Andresen, Bek, la Cour, Hajari, Heegaard, Højlund, Kawasaki, Kolko, Schielke, Rubin, Vestergaard and Grauslund involved in acquisition, analysis or interpretation of the data, critical revision of the manuscript and approval of final version. Stokholm involved in statistical analysis. Sperling involved in the drafting of the manuscript. Grauslund involved in supervision.

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CONFLICT OF INTEREST

None reported.

ETHICAL APPROVAL

This study was part of the Ocular And Systemic complications In diabetic retinopathy Study (OASIS), initiated by the Danish Excellence Centre in Ophthalmic Epidemiology (DECODE-EYE).(Grauslund et al., 2020) The study was conducted following the tenets of the Helsinki Declaration. Permissions were obtained from the Region of Southern Denmark's record of data processing activities (Journal nr. 18/61231) and the Danish Clinical Registries (DIABASE-2018-12-11). In accordance with Danish law, informed consent and permissions from the Danish National Committee on Health Research Ethics are not required for registry studies.

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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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