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Diabetic retinopathy is a predictor of chronic respiratory failure: A nationwide register-based cohort study

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ABSTRACT

Purpose: Diabetic retinopathy (DR) is a hypoxic retinal disease, but so far, the association with systemic hypoxia is poorly understood. Hence, the aim of this study was to evaluate cross-sectional and longitudinal associations between DR and chronic respiratory failure (CRF) in a national cohort.

Design: Cross-sectional and 5-year longitudinal register-based cohort study.

Methods: Between 2013 and 2018, we included patients with diabetes from the Danish Registry of Diabetic Retinopathy, who were each age and sex matched with five controls without diabetes. At index date, the prevalence of CRF was compared between cases and controls, and the longitudinal relationship between DR and CRF was assessed in a five-year follow-up.

Results: At baseline, we identified 1,980 and 9,990 patients with CRF among 205,970 cases and 1,003,170 controls. The prevalence of CRF was higher among cases than controls (OR 1.75, 95% CI 1.65–1.86), but no difference between cases with and without DR was found.

During follow-up, we identified 1,726 and 5,177 events of CRF among cases and controls, respectively. The incidence of CRF was higher among both cases with and without DR compared to controls (DR level 0: HR 1.24, 95% CI 1.16–1.33, DR level 1–4: HR 1.86, 95% CI 1.63–2.12), and higher among cases with DR compared to cases without DR (HR 1.54, 95% CI 1.38–1.72).

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Conclusion: In this study based on nationwide data, we found an increased risk of present and incident CRF in patients with diabetes with or without DR, and we identified DR as a predictor of future CRF.

1. Introduction

Diabetes is a systemic disorder with increasing global prevalence [1,2]. In 2019, the prevalence worldwide was estimated to be 9.3% (463 million people), expected to increase to 10.9% (700 million people) by 2045 [2]. Diabetes is characterized by a chronic hyperglycemic state, associated with inflammation and oxidative stress [3,4]. As a result, it leads to micro- and macro vascular damage causing hypoxia in the affected organs as e.g. the eye, causing diabetic retinopathy (DR) [4–6]; considered the most frequent complication of diabetes [7,8]. Screening of DR reduces the risk of irreversible vision loss [9,10], and screening programs have successfully been implemented in Denmark [11], among other countries [12,13].

Chronic respiratory failure (CRF) is a clinical condition in which the respiratory system fails to maintain a sufficient gas exchange leading to chronic hypoxemia (type 1 respiratory failure) without or with concurrent hypercapnia (type 2 respiratory failure) depending on the underlying chronic disease [14]. In CRF, the hypoxemia induces hypoxia in different tissues, unless oxygen therapy is initiated. CRF is often the result of end-stage chronic lung or heart diseases e.g., chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), or chronic heart failure [14–16].

Previous studies found that both pulmonary vasculature, lung parenchyma and the gas exchange can be affected by the pro-inflammatory, proliferative and oxidative properties of hyperglycemia in diabetes [4,17–19]. Ehrlich et al. [20] investigated the association between diabetes and chronic lung disease in a retrospective, longitudinal cohort study. They found that patients with diabetes had increased risk of lung diseases such as COPD, asthma, pulmonary fibrosis and pneumonia.

To our knowledge, no studies have reported the assessment of a potential association between retinal and systemic hypoxia in DR and CRF, respectively, as well as whether diabetes, complicated by microvascular disease, may increase the risk of CRF. It would be of great clinical interest to examine whether DR associates with CRF to consider if patients in DR screening with respiratory symptoms should be paid additional attention.

In this nationwide register-based cohort study we aimed to investigate the prevalence of CRF in a cohort of patients with diabetes screened for DR, and determine whether DR may predict CRF at five-year follow-up.

2. Methods

This study was conducted as a matched register-based cohort study based on data from four national Danish registries including persons with diabetes from the Danish Registry of Diabetic Retinopathy (DiaBase). The first part of the study investigated the prevalence of CRF among patients with diabetes with and without DR at index date compared with non-diabetic controls in a cross-sectional design. The second part of the study was a 5-year prospective investigation examining the incidence of CRF among patients with diabetes with or without DR compared to non-diabetic controls.

2.1. Data sources

In Denmark, healthcare is government-funded, and information regarding treatment and diagnoses is registered and saved in comprehensive national registries [21,22]. In this study, we used data from DiaBase, the Danish National Patient Register (NPR), the Danish Civil Registration System (CPR), and the Danish National Prescription Registry (DNPR). DiaBase is a national quality database containing data on all screening episodes for DR of adult patients with diabetes [23]. The DiaBase was developed between 2003 and 2006, and the systemic collection of outpatient data was extended nationwide in 2010. In 2013, data also were included from practicing ophthalmologist. Screening for DR is a tax funded service accessible to all patients with diabetes above 18 years, and results are reported to DiaBase. The level of DR is graded from 0 to 4 according to the International Clinical Retinopathy Disease Severity Scale (ICDR scale, 0 = no DR, 1–3 = mild, moderate, and severe non-proliferative DR (NPDR) and 4 = proliferative DR (PDR)) [11,24]. Screening is performed predominantly by fundus photography [8], and individualized screening intervals are used according to national guidelines [11]. NPR was established in 1977 and comprises information on a patient specific level of hospital in- and outpatient visits as well as received diagnoses and treatments, according to the International Classification of Diseases system [25–27]. In this study, data from NPR are used from 1995 and forward. CPR was established in 1968, from which we retrieved information on birth-year, sex and marital status [26,28]. DNPR was established in 1995 and contains information on all prescribed medications redeemed at community pharmacies in Denmark, date and information about discharge, drug information etc. [21] All prescribed medication is classified in accordance with the Anatomical Therapeutic Chemical (ATC) Classification System [29].

2.2. Study population

2.2.1. Cases and controls

Cases were defined as patients with diabetes screened for DR between January 1, 2013 and December 31, 2018 and thus being registered in DiaBase. Index date was defined as the first date of screening registered in DiaBase. Level of DR was defined by the highest

DR level in any eye at index date. Each case was age and sex matched with five random controls extracted from CPR. We excluded controls with diabetes if they were registered with an ICD-10 code for type 1 diabetes (E10*) or type 2 diabetes (E11*) or ATC-codes of redeemed prescriptions of non-insulin blood glucose lowering drugs (A10B*) and insulin (A10A*) at any given time during study follow-up. Patients with diabetes were excluded from the control group because diabetes is often preceded by prediabetes, and the metabolic change that distinguish them to some extend from other controls, even before we know thier diagnose. After this exclusion the final number of controls were 1,003,170 (Fig. 1). Controls were assigned the index date of their matched cases.

2.2.2. Outcomes

ICD-10 codes for respiratory failure and CRF (J961 and J969) were used as surrogate outcome measures of systemic hypoxia. In the cross-sectional part, we assessed the presence of CRF at index date and performed cross-sectional analyses, and in the prospective part, cases and controls with CRF according to NPR before index date was excluded, and incident CRF was examined.

2.2.3. Covariates

To categorize the types of diabetes, we combined ICD-10 codes for type 1 diabetes (DE10*) and type 2 diabetes (DE11*) with ATC-codes of redeemed prescriptions of oral blood glucose lowering drugs (A10B*) and insulin (A10A*) (Supplementary Table 1) [22]. Comorbidities were evaluated by the Charlson comorbidity index (CCI) modified by excluding diabetes. Otherwise, we risked that the hospital-coded cases got an artificially higher score than the controls and the non-hospital-coded cases [30,31].

2.2.4. Statistics

Descriptive statistics were presented as counts with proportions or medians with interquartile ranges (IQR). 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 and 2). DR level 1–4 was pooled in order to obtain statistical power in the analysis. In the cross-sectional study, we evaluated the presence of CRF at index date. We estimated odds ratios (ORs) with 95% confidence intervals (CIs) by a multivariable logistic regression (Table 3). Results were given in crude, age- and sex-adjusted, as well as multivariable model. In this study confounders were selected based on a priori clinical knowledge, and the multivariable regression was adjusted for sex, age, marital status, use of anti-hypertensive medications and use of cholesterol lowering medications at index date. In the prospective study follow-up duration was calculated as the time between index date and date of event (CRF), death, migration or censoring at December 31st, 2018, whichever came first. We estimated hazard ratios (HRs) with 95% CI by Cox regression for incident CRF among persons with diabetes with and without DR compared to controls (Table 4). The multivariable model in the prospective study was adjusted for sex, age, marital status, use of anti-hypertensive medications and use of cholesterol lowering medications at index date. Further inclusion of CCI in the model only caused

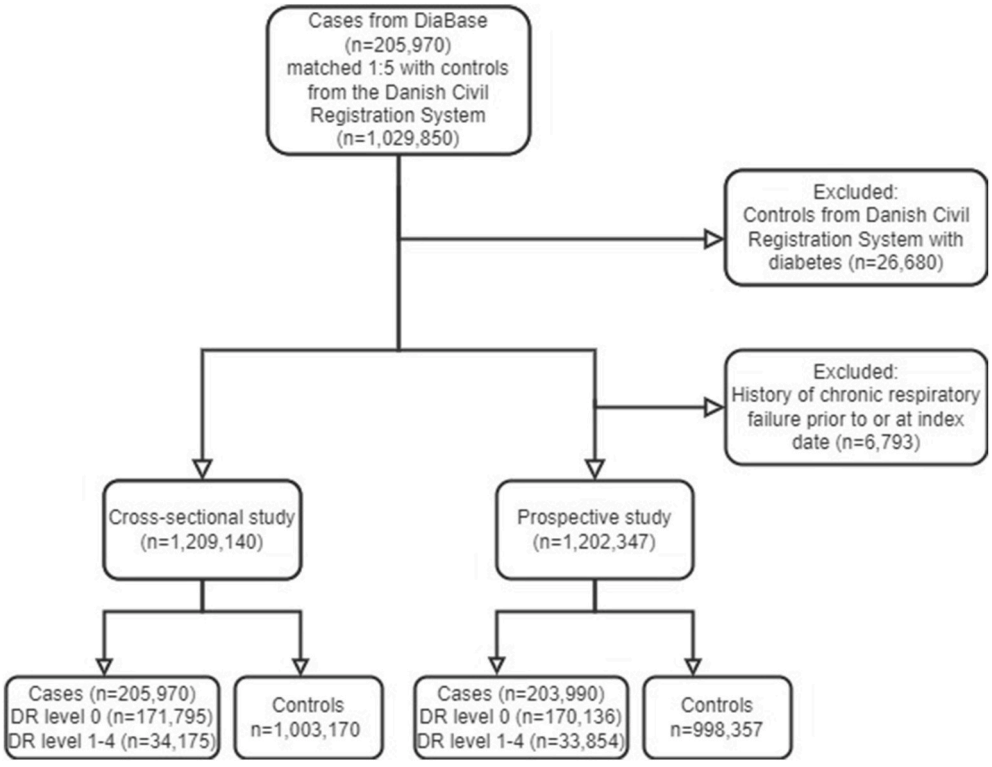

Fig. 1. Flowchart of the selection of study participants for the different parts of the study. DR, diabetic retinopathy.

Table 1
Characteristics of patients with diabetes at the first occurrence in DiaBase according to level of diabetic retinopathy.

	Overall	Level of DR				
		Level 0	Level 1	Level 2	Level 3	Level 4
Number of patients, n	205970	171795	21131	6594	1162	5288
Sex, n (%) male	116534 (56.6)	95843 (55.8)	12522 (59.3)	4159 (63.1)	787 (67.7)	3223 (60.9)
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)
Type of diabetes, n (%)						
Type 1 diabetes	16999 (8.3)	9490 (5.5)	4571 (21.6)	1132 (17.2)	228 (19.6)	1578 (29.8)
Type 2 diabetes	153238 (74.4)	139700 (81.3)	9495 (44.9)	2682 (40.7)	419 (36.1)	942 (17.8)
Unknown	35733 (17.3)	22605 (13.2)	7065 (33.4)	2780 (42.2)	515 (44.3)	2768 (52.3)
Duration of diabetes, years (IQR)[a]						
Type 1 diabetes	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 diabetes	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, n (%)						
Never married	30904 (15.0)	24524 (14.3)	3775 (17.9)	1247 (18.9)	283 (24.4)	1075 (20.3)
Married or living with someone	118764 (57.7)	99847 (58.1)	11820 (55.9)	3634 (55.1)	588 (50.6)	2875 (54.4)
Widowed or divorced	56302 (27.3)	47424 (27.6)	5536 (26.2)	1713 (26.0)	291 (25.0)	1338 (25.3)
Charlson Comorbidity Index score, n (%)[b]						
0 (low)	148615 (72.2)	129907 (75.6)	12730 (60.2)	3555 (53.9)	576 (49.6)	1847 (34.9)
1 (moderate low)	27728 (13.5)	18248 (10.6)	5010 (23.7)	1892 (28.7)	387 (33.3)	2191 (41.4)
2 (Moderate high)	18721 (9.1)	15436 (9.0)	1852 (8.8)	615 (9.3)	114 (9.8)	704 (13.3)
≥3 (high)	10906 (5.3)	8204 (4.8)	1539 (7.3)	532 (8.1)	85 (7.3)	546 (10.3)
Use of medication, n (%)						
Insulin	68285 (33.2)	43348 (25.2)	14386 (68.1)	4978 (75.5)	917 (78.9)	4656 (88.0)
Glucose lowering treatment, excl. insulins	155345 (75.4)	136389 (79.4)	12470 (59.0)	3997 (60.6)	665 (57.2)	1824 (34.5)
Antihypertensive drugs	154305 (74.9)	127960 (74.5)	15863 (75.1)	5072 (76.9)	861 (74.1)	4549 (86.0)
Cholesterol lowering drugs	152205 (73.9)	127685 (74.3)	15083 (71.4)	4693 (71.2)	780 (67.1)	3964 (75.0)

DR, diabetic retinopathy; IQR, interquartile range; n, count; N/A, not applicable.

[a] The duration of diabetes was defined as the difference between the earliest registration of an International Classification of Diseases version 10 code for diabetes or redeemed prescription of oral glucose-lowering drugs or insulin and the index date in DiaBase. Among all cases, 6% had missing information in duration of diabetes.

[b] CCI was modified by excluding diabetes.

minor changes in HR (data not shown). As a supplementary analysis, we evaluated the incidence of CRF among cases with DR compared to cases without DR (Table 5). Likewise, we modeled a competing risk analysis with death as a competing cause to CRF [32]. Lastly, incident DR where examined among patients with CRF at index-date in a prospective analysis.

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.

2.2.5. Ethics committee approval and informed consent

This study was part of the Ocular And Systemic complications In DR Study (OASIS) initiated by the Danish Excellence Centre in Ophthalmic Epidemiology (DECODE-EYE) [33], and the study design may be comparable to other studies included in OASIS [22,28,34]. 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 register-based studies.

The study was conducted in accordance with the tenets of the Helsinki Declaration.

3. Results

3.1. Patients' characteristics

The analyses were based on a cohort of 1,209,140 individuals, of which 205,970 cases had diabetes and were registered in DiaBase and 1,003,170 controls did not.

For cases, the median age was 65.7 years (interquartile range (IQR) 55.4–73.1 years) and 56.6% were men, who were more likely to be diagnosed with type 2 diabetes (74.4%). Controls with CRF were older than controls without CRF and cases with and without CRF (72.8 years (IQR 66.2–79.1 years)). The median duration of diabetes at index date were 5.3 years (IQR 2.1–9.8 years) for patients with type 2 diabetes and 16.7 years (IQR 7.4–20.4 years) for patients with type 1 diabetes. We found a tendency for the duration of diabetes to be longer with increasing levels of DR and that cases with low level of DR had a lower CCI. The CCI increased with increasing level of DR alongside the use of insulin (Table 1). Of underlying diagnoses of CRF, 57.3% were diagnosed with COPD (Supplementary Table 2),

Table 2
Differences between cases and controls with and without chronic respiratory failure at index date.

	Case population		Control population	
	CRF	No CRF	CRF	No CRF
Number of patients, n (%)	1980	203990	4813	998357
Sex, n (%) male	1132 (57.2)	115402 (56.6)	2772 (57.6)	563971 (56.5)
Age, years (IQR)	67.6 (59.4; 74.4)	65.7 (55.4; 73.1)	72.2 (65.1; 78.9)	65.6 (55.3; 73.0)
Type of diabetes, n (%)				
Type 1 diabetes	69 (3.5)	16930 (8.3)	N/A	N/A
Type 2 diabetes	1207 (61.0)	152031 (74.5)	N/A	N/A
Unknown	704 (35.6)	35029 (17.2)	N/A	N/A
Duration of diabetes, years (IQR)[a]				
Type 1 diabetes	16.8 (4.6; 21.0)	16.7 (7.4; 20.4)	N/A	N/A
Type 2 diabetes	5.1 (1.8; 9.7)	5.3 (2.1; 9.8)	N/A	N/A
Unknown	12.9 (8.2; 18.1)	14.0 (8.4; 19.2)	N/A	N/A
Marital status, n (%)				
Never married	308 (15.6)	30596 (15.0)	628 (13.0)	136977 (13.7)
Married or living with someone	928 (46.9)	117836 (57.8)	2167 (45.0)	609126 (61.0)
Widowed or divorced	744 (37.6)	55558 (27.2)	2018 (41.9)	252254 (25.3)
Charlson Comorbidity Index score (CCI), n (%)[b]				
0 (low)	503 (25.4)	148112 (72.6)	1444 (30.0)	862542 (86.4)
1 (moderate low)	542 (27.4)	27186 (13.3)	1645 (34.2)	44719 (4.5)
2 (moderate high)	314 (15.9)	18407 (9.0)	664 (13.8)	69630 (7.0)
≥3 (high)	621 (31.4)	10285 (5.0)	1060 (22.0)	21466 (2.2)
Use of medication, n (%)				
Insulin	885 (44.7)	67400 (33.0)	N/A	N/A
Glucose lowering treatment, excl. insulins	1495 (75.5)	153850 (75.4)	N/A	N/A
Antihypertensive drugs	1596 (80.6)	152709 (74.9)	2651 (55.1)	371942 (37.3)
Cholesterol lowering drugs	1488 (75.2)	150717 (73.9)	1617 (33.6)	231485 (23.2)
Level of diabetic retinopathy (diabetic retinopathy), n (%)				
0	1659 (83.8)	170136 (83.4)	N/A	N/A
1	208 (10.5)	20923 (10.3)	N/A	N/A
2	56 (2.8)	6538 (3.2)	N/A	N/A
3	<5	1158 (0.6)	N/A	N/A
4	>52	5235 (2.6)	N/A	N/A

Results are given as number (%) or median (IQR).
CRF, chronic respiratory failure.
[a] The duration of diabetes was defined as the difference between the earliest registration of an ICD-code for diabetes or redeemed prescription of oral glucose-lowering drugs or insulin and the index date in DiaBase. Among all cases, 6% had missing information in duration of diabetes.
[b] CCI was modified by excluding diabetes.

Table 3
Odds ratio with 95% confidence interval for CRF at index date among patients screened for diabetic retinopathy, compared to a 1:5 age- and sex-matched control population without diabetes.

Level of DR	Cases		Controls[b]		Crude model	Model adjusted for Sex and age	Multivariable model[a]
	Persons with CRF	Persons without CRF	Persons with CRF	Persons without CRF	OR (95% CI)	OR (95% CI)	OR (95% CI)
Overall	1980	203,990	4813	998,357	2.01 (1.91; 2.12)	2.01 (1.91; 2.12)	1.75 (1.65; 1.86)
Level 0	1659	170,136	4096	832,769	1.98 (1.87; 2.10)	1.98 (1.87; 2.10)	1.74 (1.63; 1.86)
Level 1-4	321	33,854	717	165,588	2.19 (1.92; 2.50)	2.19 (1.91; 2.49)	1.78 (1.53; 2.08)

Results are given as number or OR (95% CI).
Controls do not have DR but they are matched controls of cases.
CI, confidence interval; DR, diabetic retinopathy; OR, odds ratio; CRF, chronic respiratory failure.
[a] Multivariable logistic regression model adjusted for sex, age at first screening, marital status, use of anti-hypertensive medication and use of cholesterol lowering medication.

Table 4
Hazard ratio with 95% confidence interval for chronic respiratory failure after index date for patients screened for diabetic retinopathy compared to a 1:5 age- and sex-matched control population without diabetes.

Level of DR	Cases		Controls[b]		Crude model	Model adjusted for sex and age	Multivariable model[a]
	Events of CRF	Years of risk	Events of CRF	Years of risk	HR (95% CI)	HR (95% CI)	HR (95% CI)
All	1726	657,035	5177	3,218,986	1.63 (1.55; 1.72)	1.62 (1.53; 1.71)	1.35 (1.27; 1.43)
0	1300	529,942	4271	2,582,881	1.48 (1.39; 1.58)	1.46 (1.38; 1.56)	1.24 (1.16; 1.33)
1–4	426	127,092	906	636,105	2.35 (2.10; 2.64)	2.36 (2.11; 2.65)	1.86 (1.63; 2.12)
1	261	78,295	555	388,096	2.33 (2.01; 2.70)	2.33 (2.01; 2.70)	1.78 (1.51; 2.10)
2	71	24,387	169	122,486	2.11 (1.60; 2.79)	2.14 (1.62; 2.83)	1.81 (1.32; 2.48)
3	14	4,230	23	21,530	3.10 (1.60; 6.03)	3.21 (1.65; 6.25)	1.97 (0.92; 4.22)
4	80	20,178	159	103,993	2.58 (1.97; 3.38)	2.62 (2.00; 3.42)	2.25 (1.64; 3.10)

Results are given as number or HR (95% CI).
CI, confidence interval; DR, diabetic retinopathy; HR, hazard ratio; CRF, chronic respiratory failure.
[a] Multivariable Cox regression model adjusted for sex, age at first screening, marital status, use of anti-hypertensive medication and use of cholesterol lowering medication.
[b] Controls do not have DR but are matched controls of the cases.

Table 5
Hazard ratio with 95% confidence interval for chronic respiratory insufficiency after index date for cases with diabetic retinopathy compared to cases with diabetes but no diabetic retinopathy (level 0).

Level of DR	Cases		Crude model	Model adjusted for sex and age	Multivariable model[a]
	Events of CRF	Years of risk	HR (95% CI)	HR (95% CI)	HR (95% CI)
0	1300	529,942	ref	ref	ref
1–4	426	127,092	1.37 (1.23; 1.53)	1.57 (1.40; 1.75)	1.54 (1.38; 1.72)
1	261	78,296	1.36 (1.19; 1.55)	1.52 (1.33; 1.73)	1.50 (1.31; 1.71)
2	71	243,88	1.19 (0.93; 1.51)	1.37 (1.08; 1.74)	1.35 (1.06; 1.71)
3	14	4,231	1.34 (0.79; 2.28)	1.91 (1.13; 3.25)	1.87 (1.10; 3.18)
4	80	20,178	1.62 (1.29; 2.03)	1.93 (1.54; 2.42)	1.88 (1.50; 2.36)

Results are given as number or HR (95% CI).
CI, confidence interval; DR, diabetic retinopathy; HR, hazard ratio; CRF, chronic respiratory failure; ref, reference.
[a] Multivariable Cox regression model adjusted for sex, age at first screening, marital status, use of anti-hypertensive medication and use of cholesterol lowering medication.

and 26.3% of patients with CRF had no diagnoses based on CCI, 33.5% had one diagnosis, and the rest had two or more diagnoses based on CCI (data not shown).

3.2. Cross-sectional part

At index date 1,980 cases and 4,813 controls had a diagnosis of CRF, respectively (Table 2). Cases with CRF were less likely to have type 1 diabetes (3.5% vs. 8.3%) and type 2 diabetes (61.0% vs. 74.6%) compared to cases without CRF whereas 35.6% of cases with CRF and 17.0% without CRF were categorized with unknown type of diabetes. For both cases and controls, those with CRF were more likely to be older, widowed or divorced, use cholesterol lowering and antihypertensive drugs and have a higher CCI ($P < 0.001$). In a multivariable logistic regression, we found an increased adjusted odds for CRF among cases with DR compared to controls (adjusted OR 1.75, 95% CI 1.65–1.86), as well as when cases with and without DR were compared to controls separately (DR level 1–4: adjusted OR 1.78, 95% CI 1.53–2.09, DR level 0: adjusted OR 1.74, 95% CI 1.63–1.86) (Table 3).

3.3. Prospective part

Of the 6,903 events of CRF during follow-up, 1,300 events occurred among cases without DR, 426 events of CRF in the case group with DR and 5,177 events in the control group (Table 4). In a multivariable Cox regression we found an increased hazard of CRF among all cases compared to controls (adjusted HR 1.35, 95% CI 1.27–1.43), as well as when cases with and without DR were compared to controls separately (DR level 1–4: adjusted HR 1.86, 95% CI 1.63–2.12, DR level 0: adjusted HR 1.24, 95% CI 1.16–1.33). Furthermore, we found a tendency for the hazard of CRF to increase with the level of DR (Table 4). The sub hazard for CRF, when taking into account the competing risk of death, was increased compared to controls (HR 1.50, 95% CI 1.38–1.64). The incidence of CRF (426/127,092 years) among cases with DR increased with 54% (adjusted HR 1.54, 95% CI 1.38–1.72) compared to cases without DR, with a tendency for the hazard of CRF to increase with the level of DR (DR level 1: adjusted HR 1.50, 95% CI 1.31–1.71, DR level 4: adjusted HR 1.88, 95% CI 1.50–2.36) (Table 5). In a separate multivariable analysis, the risk of incident DR did not differ between cases with and without CRF at index date (90 events in 2988 person-years versus 13,162 events in 413,268 person-years, adjusted HR 0.97, 95% CI 0.79–1.19).

4. Discussion

Based on this national register-based cohort study including more than 1.2 million Danish citizens, we found that patients with diabetes screened for DR had an increased prevalence of CRF of 75% compared to individuals without diabetes. Furthermore, we found a five-year risk of incident CRF among patients with DR was increased by 86% compared to controls and correspondingly 54% compared to patients with diabetes and no DR.

Initially, the pathophysiological association between retinal hypoxia and systemic hypoxia described in the following studies led to the idea that DR and CRF might be positively correlated. Palkovits et al. [35] found a strong correlation between retinal and peripheral arterial oxygen saturation among patients with severe COPD in need of long-term oxygen therapy, and Eliasdottir et al. [36] found that patients with COPD and no diabetes had significantly lower saturation in both retinal arterioles and venules than healthy controls. These studies contribute to the idea that systemic hypoxia associates with existing retinal hypoxia. Traustason et al. [37] found that patients with Eisenmenger syndrome who showed systemic hypoxia also had decreased retinal arterial and venous saturation. Like patients with Eisenmenger syndrome, patients with CRF suffered from some level of systemic hypoxia, even for an extended period before the time of diagnosis [38–40]. Therefore, we might speculate that this is also true before the diagnosis of DR in our included cases.

Based on the register-based setup of this study, we cannot derive a pathophysiological explanation; nevertheless, our data supports the hypothesis that affection of minor retinal vessels may precede clinical significant affection of major vessels in other tissues such as the lungs and heart. Contrary to the retinal blood vessels, the lungs possess two vessel systems; the pulmonary and bronchial vessels, making the lungs potentially less susceptible of hypoxia [41]. On the other hand, we know that poor glycemic control in patients with diabetes increases the risk of progression in DR, and patients with a high level of DR have an increased risk of general microvascular disease [42] as well as higher comorbidity according to CCI in our data. Whether this microvascular impact of diabetes also affects the microvasculature of the lungs and increases the risk of lung induced hypoxemia with CRF, may be considered. Therefore, diabetes could be considered as a possible confounder in the association between DR and CRF, which may also add to the explanation of why CRF was more prevalent in patients with diabetes at index date compared to patients without diabetes, but had no relation to the presence or absence of DR. However, a diagnosis of type 2 diabetes will warrant an immediate advice to begin screening and a diagnosis of type 1 diabetes warrants the advice to begin screening after 5 years [11] and thus the systemic impact on peripheral blood vessels and tissues may therefore be relatively low at index date. In addition, we found a higher incidence of CRF among patients with DR compared to patients with diabetes and no DR, which indicate that diabetes itself, is not the entire explanation.

Despite the consideration that long-term systemic hypoxia associates with hypoxia in the retina, the full pathophysiology is not entirely understood and more clinical trials in this area of research are warranted.

5. Strengths and limitations

A clear strength of this study includes the population-based approach with high completeness of data, in a large nationwide register based cohort of patients attending diabetic eye screening. We had a broad range of information regarding DR level as well as systemic comorbidity and medications, as given by a variety of national registers. Furthermore, we were able to perform a longitudinal estimate of DR as a marker of incident CRF, including almost four million years of risk time. Finally, the levels of DR specified in DiaBase are recently validated, supporting the strength of the database for this study [43].

Limitations of the study are also essential to acknowledge. First, the CRF diagnosis always has an underlying diagnosis [14], where we used the NPR for evaluation. Some difficulties defining the exact underlying diagnosis for all cases were present. In general, the patients with CRF are a diverse group with very different underlying illnesses treated with many different medications, which might possibly influence the occurrence of diabetes among other chronic diseases. Likewise, the competing risk analysis revealed an increased risk of all-cause mortality before CRF, which emphasizes that this group of patients has severe underlying disorders. The gravity and complexity in the underlying diagnoses were also the reason why we refrained from adjusting for comorbidities by CCI in the regressions, as the risk of over-adjusting was likely. From a clinical perspective, it was better to under-adjust and annotate at the population level, as it was difficult to determine which covariates were confounders and which mediating factors.

Second, we cannot deduce whether the difference in CCI is solely causally conditioned or if it is due to the doubtless stronger hospital connection for patients with CRF, which might give them a greater chance of suitable medical treatment of comorbidities. Third, we have to acknowledge that several lung- and heart diseases are associated to both CRF and smoking [44,45], and pathophysiologically smoking associates to diabetes [46]. However, a previous study found neither beneficial nor a harmful effect of smoking on long-term incidence of DR [47]. Based on the available register data we did not have the opportunity to adjust for smoking as a potential confounder. Likewise we did not have the opportunity to adjust for other lifestyle factors as body mass index, diet and exercise beside blood sugar level in patients with diabetes. These factors might influence outcome as well, and one could speculate that the odds ratio would be lower when adjusting for such factors in the analyses.

Fourth, information on exact hyperglycemia measurements as well as the degree of CRF were not available in the registers used in this study. Fifth, we acknowledge that our control population may have some selection bias, as we excluded individuals who developed diabetes during follow up. However, we did not aim to make a comparison to the general Danish population, only to patients without diabetes due to the pathophysiologic characteristic because diabetes is often preceded by prediabetes, and the metabolic changes that distinguish them to some extend from other controls, even before their diagnosis is registered. Nevertheless, it is possible that some cases of diabetes is still included within the reference group since the registers that we used do not include data from general practitioners where patients with mild cases of diabetes who are managing their disease exclusively through diet and lifestyle changes are

treated. Likewise, consideration must be given to the fact that we only had access to the 205,970 patients with diabetes who attended DR screening out of estimated 280,000 patients with diabetes in Denmark [48], and thus a risk of selection bias is present, as one could speculate that the patients with a more significant disease burden from diabetes or CRF, might not attend screening at all.

In conclusion, these observational findings indicate that DR may act as a marker of CRF, since diabetes and especially DR are associated with the occurrence of CRF. Increased attention to respiratory symptoms in patients with DR should be given and further pulmonary medical investigation may be considered.

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Author contribution statement

Benjamin Sommer Thinggaard - Conceived and designed the experiments, Performed the experiments, Analyzed and interpreted the data, Contributed reagents, materials, analysis tools or data, Wrote the paper.

Lonny Stokholm - Conceived and designed the experiments, Performed the experiments, Analyzed and interpreted the data, Contributed reagents, materials, analysis tools or data, Wrote the paper.

Jesper Rømhild Davidsen - Conceived and designed the experiments, Performed the experiments, Analyzed and interpreted the data, Contributed reagents, materials, analysis tools or data, Wrote the paper.

Maria Carius Larsen - Performed the experiments, Analyzed and interpreted the data, Contributed reagents, materials, analysis tools or data.

Sören Möller - Analyzed and interpreted the data, Contributed reagents, materials, analysis tools or data.

Anne Suhr Thykjær - Analyzed and interpreted the data, Contributed reagents, materials, analysis tools or data, Wrote the paper.

Jens Lundgaard Andresen - Analyzed and interpreted the data, Contributed reagents, materials, analysis tools or data.

Nis Andersen - Analyzed and interpreted the data, Contributed reagents, materials, analysis tools or data.

Steffen Heegaard - Analyzed and interpreted the data, Contributed reagents, materials, analysis tools or data.

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Caroline Laugesen - Analyzed and interpreted the data, Contributed reagents, materials, analysis tools or data.

Toke Bek - Analyzed and interpreted the data, Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e17342.

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