AMERICAN ACADEMY OF OPHTHALMOLOGY®

Inverse Cross-sectional and Longitudinal Relationships between Diabetic Retinopathy and Obstructive Sleep Apnea in Type 2 Diabetes

Results from a National Screening Program

Jakob Grauslund, DMSci,[1,2,3] Lonny Stokholm, PhD,[2,4] Anne S. Thykjær, MD,[1,2,3] Sören Möller, PhD,[2,4] Caroline S. Laugesen, MD,[5] Jens Andresen, PhD,[6] Toke Bek, DMSci,[7] Morten la Cour, DMSci,[8,9] Steffen Heegaard, DMSci,[8,9] Kurt Højlund, DMSci,[2,3] Ryo Kawasaki, PhD,[2,10] Javad Hajari, PhD,[8,9] Kirsten O. Kyvik, PhD,[2] Katja C. Schielke, MD,[11] Katrine H. Rubin, PhD,[2,4] Malin L. Rasmussen, PhD[1,2]

Purpose: In previous smaller studies, associations were demonstrated between diabetic retinopathy (DR) and obstructive sleep apnea (OSA), but longitudinal relationships have not been evaluated in larger cohorts. The aim of the present study was to assess the cross-sectional and prospective associations between DR and OSA in a national cohort of patients with type 2 diabetes.

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

Participants: For cases, we included 153 238 patients with type 2 diabetes who had attended diabetic eye screening and were registered in the Danish Registry of Diabetic Retinopathy (DiaBase). Each of these were matched by 5 control participants without diabetes of the same age and gender (n = 746 148).

Methods: Exposure and outcome data as well as systemic morbidity and use of medications were identified in national registers, including the DiaBase, the Danish National Patient Register, the Danish National Prescription Registry, and the Danish Civil Registration System. The index date was defined as the date of the first DR screening registered in DiaBase.

Main Outcome Measures: Exposure was defined as present and level-specific DR, and main outcomes were crude, age- and gender-adjusted, and multivariable adjusted odds ratios (ORs) for prevalent OSA as well as hazard ratios (HR) for 5-year incident OSA and DR.

Results: Patients with type 2 diabetes independently were more likely to have prevalent OSA (OR, 2.01; 95% confidence interval [CI], 1.95−2.08) and to develop OSA within 5 years (HR, 1.55; 95% CI, 1.46−1.64). Patients with type 2 diabetes and DR at baseline were less likely to have prevalent OSA (OR, 0.57; 95% CI, 0.52−0.62) or to demonstrate incident OSA (HR, 0.86; 95% CI, 0.74−0.99). Likewise, patients with OSA had a lower risk to develop DR (HR, 0.83; 95% CI, 0.74−0.92).

Conclusions: In a registry-based national cohort study, patients with type 2 diabetes had a higher risk of OSA. However, a 43% decreased risk of prevalent OSA was demonstrated in patients with DR, and prospectively, OSA and DR both were related inversely with each other. *Ophthalmology Science 2021;1:100011 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Diabetic retinopathy (DR) is the most common complication in diabetes[1,2] and a leading cause of blindness in the diabetes population.[3,4] Screening of DR is highly recommended to reduce the risk of irreversible visual loss,[5,6] and this has been implemented successfully in Denmark[7] and other countries.[8,9]

Obstructive sleep apnea (OSA) is a devastating sleep disorder associated with chronic intermittent nocturnal hypoxemia, arousal, and sleep fragmentation.[10] In a meta-analysis, Qie et al[11] demonstrated that patients with type 2 diabetes are 40% more likely to have OSA compared with patients without diabetes, and likewise, patients with type 2 diabetes and moderate to severe OSA are 3 times more likely to experience microvascular and macrovascular diabetes related-complications.[12]

An association between DR and OSA has been proposed, given the pathophysiologic similarities between the conditions. Systemic hypoxia in OSA may activate oxidative stress and promote inflammatory pathways, which may increase levels of vascular endothelial growth factor,[13] thereby promoting DR.[14] In a meta-analysis, Leong et al[10] found

https://doi.org/10.1016/j.xops.2021.100011
ISSN 2666-9145/21

some evidence that OSA may be associated with higher levels of DR, but most of these studies were cross-sectional and included low numbers of patients.[15] In fact, we are aware of only 1 prospective study of 121 patients that, during 43 months of follow-up, demonstrated a 5.2-fold increase of incident advanced DR in those with OSA present at baseline.[16]

From a clinical point of view, it also is important to examine whether DR is able to act as a predictive marker for OSA, given that early detection and treatment of OSA may be cost-effective[17] and may halt the progression of DR, as demonstrated by Altaf et al.[16] Thus, based on the hypothesis that DR may act as an independent marker of systemic neurovascular dysfunction, which may cause OSA in type 2 diabetes, the present study aimed to evaluate the role of DR in the development of incident OSA in a national cohort of patients with type 2 diabetes. Likewise, we tested if the presence of OSA had an influence on the future development of DR.

Methods

Study Population

In Denmark, screening for DR has been implemented since 2013. It is offered for free for all patients with diabetes, and the screening program can be attended either at the offices of practicing ophthalmologists or at selected hospital departments. Screening is performed predominantly by fundus photography according to a national guideline, stating that (1) screening should as a minimum be performed based on mydriatic 2-field retinal images, (2) the level of DR should be graded according to the International Clinical Retinopathy Disease Severity Scale[18] as levels 0 (no DR), 1 through 3 (mild, moderate, and severe nonproliferative DR) or 4 (proliferative DR), and (3) flexible, individualized screening intervals should be used.[7]

It is mandatory to report screening results to the Danish Registry of Diabetic Retinopathy (DiaBase), which is a national quality database including data from 591 136 screening episodes of 205 970 patients who attended the screening program.[19] The DiaBase comprises all patients older than 18 years diagnosed with diabetes in Denmark, who have attended the DR screening program. The DiaBase was developed between 2003 and 2006, and the systematic collection of outpatient data from hospitals in Denmark started in 2008 and was extended nationwide in 2010. In 2013, data also were included from practicing ophthalmologists, who perform the screening for most patients.[19] For both eyes, the DiaBase includes the level of DR, visual acuity, presence or absence of diabetic macular edema, prior eye surgery (cataract extraction and vitrectomy), and planned interval to next eye screening.

In the present study, we included data of patients with type 2 diabetes collected between January 2, 2013, and December 28, 2018. The index date was set as the date of the first registration in DiaBase, and each patient was matched by year of birth and gender with 5 control participants who were not registered in DiaBase. Control participants were excluded if they had been diagnosed with an International Classification of Diseases, Tenth Revision (ICD-10), code for diabetes at the index date. Level of DR at the time of the index date was given by the highest level of the 2 eyes of the patient.

In the cross-sectional part of the study, we evaluated presence of OSA at the time of the index date in accordance with level of DR. In the prospective study, patients and control participants with OSA at the index date were excluded, and incident OSA was registered with time of risk, as defined by time from the index date to incident OSA, death, emigration, or the end of the study (December 31, 2018), whichever came first. For the other part of the prospective study, we included type 2 diabetic patients without DR at baseline and registered the numbers of incident cases of DR as well of person-years at risk for patients with and without baseline OSA.

Data Extraction

National registers were used for data linkage and to register OSA and other relevant medical conditions and systemic medications. The Danish Civil Registration System was used to link data from the various registers by a unique personal identifier, the Central Personal Registration number, which is given to each inhabitant in Denmark.[20] This register was also used to obtain data regarding age, gender, and marital status.

We used the Danish National Patient Register, which includes the ICD-10 codes[21] of all hospital contacts in Denmark.[22] This register was used to identify patients with OSA (sleep apnea, G473*) and systemic comorbidity. The latter was evaluated by a modified Charlson comorbidity index score that excluded diabetes (which was present only in patients with diabetes according to study protocol), but included myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, rheumatologic disease, ulcer disease, mild or moderate to severe liver disease, hemiplegia or paraplegia, moderate or severe renal disease, any malignancies (including leukemia and lymphoma), and acquired immunodeficiency syndrome. The comorbidity was evaluated 5 years before the index date, and levels 0 through 3 reflected higher levels of comorbidity.[23,24]

We used the Danish National Prescription Registry[25] to assess the use of systemic medications as given by the Anatomical Therapeutic Chemical classification system.[26] The register included information regarding filed prescription dispensed at Danish community pharmacies. We extracted data regarding the current use of insulin (A10A*), blood glucose-lowering drugs excluding insulins (A10B*), antihypertensive treatment (C03*, C07*, C08*, and C09*), or lipid-lowering therapy (C10*).

Combining data from the Danish National Patient Register and the Danish National Prescription Registry, we were able to identify patients with type 2 diabetes in DiaBase. This was achieved by combining ICD-10 codes for type 2 diabetes (E11*) and Anatomical Therapeutic Chemical codes for redeemed prescriptions for insulin and noninsulin blood glucose-lowering drugs. Seven combinations were used for type 2 diabetes classification: DE11* only, A10B* only, DE11* and A10A*, DE11* and A10B*, A10A* and A10B*, DE11* and A10A* and A10B*, and no codes given. Patients with other combinations were excluded from this study for having type 1 diabetes or a combination of diagnostic codes and Anatomical Therapeutic Chemical codes that did not make it possible to categorize them as having type 2 diabetes.

Combined data from these 2 registers also were used to define obesity, which was defined for all persons with codes E66 (obesity) or Z98 (intestinal anastomosis) in combination with relevant surgical codes for volume-reducing operations: KJDF, KJAW90, KJAW91, KJDW96A or KJDW97A[27]; MA08AA03 (amfepramon); MA08AA62 (bupropion or naltrexon); MA08AB01 (orlistat); or MA10BJ02 (liraglutide, only including the trade name Saxenda).

Duration of diabetes was given by the difference between the index date and the date of the first ICD-10 code for diabetes or the first redeemed prescription for diabetes, whichever came first.

Statistical Analysis

Data are given as numbers, percentages, or medians (with interquartile ranges). Differences between groups in Tables 1 and 2 were estimated by the k-sample test for equality of medians (continuous data) and chi-square tests (categorical data).

Present and level-specific DR at the index date was used as a predictor, and prevalent and incident OSA was used as the outcome. In the cross-sectional part of the study (Tables 3 and 4), we estimated odds ratios (ORs) with 95% confidence intervals (CIs) for OSA in crude, age- and gender-adjusted, and multivariable logistic regression models (adjusted for all parameters with $P < 0.10$ in Table 2). Correspondingly, the prospective part of the study (Tables 5 and 6) evaluated hazard ratios (HRs) for incident OSA in crude, age- and gender-adjusted, and multivariable Cox regression models (adjusted for all parameters with $P < 0.10$ in Table 2). For references, we used the control population in Tables 3 and 5 and patients without DR in Tables 4 and 6. Finally, we used the proportion of the patient population with at least 2 screening episodes and no DR at baseline to test whether the presence of OSA at the index date would influence future development of DR (Table 7).

The proportional hazard assumptions were checked visually by log-log plots of survival. As a sensitivity analysis, we modeled a competing risk analysis with deaths as a competing cause to OSA.[28] Finally, to consider the potentially confounding effect of obesity, we performed stratified analyses, separating persons with and without obesity.

Statistical analyses were performed with Stata software version 16.1 (StataCorp LP). *P* values of less than 0.05 and CIs that did not include 1.0 were considered statistically significant.

Informed Consent and Ethics Committee Approval

The present study was part of the Ocular and Systemic Complications in Diabetic Retinopathy Study, which was initiated by the Danish Excellence Centre in Ophthalmic Epidemiology.[29] The study was performed with respect to the tenets of the Declaration of Helsinki, with permissions obtained from the record of data processing activities at the Region of Southern Denmark (identifier, 18/61231) and the Danish Clinical Registries (DIABASE-2018-12-11). According to Danish law, informed consent and permissions from the Danish National Committee on Health Research Ethics are not required for register-based studies.

Results

We identified 153 238 patients with type 2 diabetes, who had attended diabetic eye screenings and were registered in DiaBase (Table 1). Median age was 66.9 years (interquartile range, 58.0–73.8 years), 56.4% were men, and 32.0% were registered as obese. In general, patients with higher levels of DR were more likely to be men, to have a longer duration of diabetes, to be living alone, to have a higher Charlson comorbidity index score, and to use insulin and antihypertensive drugs. In contrast, a higher prevalence of OSA was found for patients with a lower level of DR

Table 1. Characteristics for Patients with Type 2 Diabetes at the First Time of Screening for Diabetic Retinopathy According to the Level of Diabetic Retinopathy as Given by the Danish Registry of Diabetic Retinopathy

		Level of Diabetic Retinopathy					
	Overall	*Level 0*	*Level 1*	*Level 2*	*Level 3*	*Level 4*	**P Value**
No. of patients	153 238	139 700	9495	2682	419	942	
Gender, % male	56.4	55.8	61.8	64.0	69.7	65.3	< 0.001
Age (yrs), median (IQR)	66.9 (58.0–73.8)	66.9 (58.0–73.8)	67.4 (58.5–74.6)	64.6 (55.8–72.2)	59.7 (52.2–67.8)	67.7 (59.1–74.8)	< 0.001
Duration of diabetes (yrs), median (IQR)*	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)	< 0.001
Marital status, %							< 0.001
Never married	12.5	12.2	13.9	16.5	15.8	18.5	
Married or living with someone	59.3	59.6	57.2	55.8	57.3	56.4	
Widowed or divorced	28.2	28.2	28.9	27.7	27.0	25.2	
Charlson comorbidity index score, %							< 0.001
0 (low)	77.2	78.2	69.4	65.6	58.5	55.4	
1 (moderate low)	10.0	9.2	16.5	19.5	25.3	27.7	
2 (moderate high)	8.7	8.7	8.8	8.7	9.5	9.9	
3 or more (high)	4.1	3.9	5.3	6.2	6.7	7.0	
Use of medication, %							
Insulin	15.8	13.3	37.3	48.6	51.1	51.6	< 0.001
Glucose-lowering treatment, excluding insulins	86.5	86.2	89.9	90.7	91.9	85.8	< 0.001
Antihypertensive drugs	77.8	77.2	83.6	82.7	81.4	89.6	< 0.001
Cholesterol-lowering drugs	77.3	77.2	79.0	77.3	75.9	78.6	0.013
Obesity, %	32.0	31.1	40.0	43.5	47.5	38.4	< 0.001
Obstructive sleep apnea, %	5.8	5.9	4.2	3.1	4.1	2.9	< 0.001

IQR = interquartile range.
*Duration of diabetes was calculated only in patients with at least 1 International Classification of Diseases, Tenth Revision, code for diabetes or 1 Anatomical Therapeutic Chemical Classification code for treatment of diabetes.

Table 2. Characteristics of Patients with Type 2 Diabetes and Control Participants without Diabetes with and without Obstructive Sleep Apnea at the Time of the First Registration in the Danish Registry of Diabetic Retinopathy for Patients

	Patient Population			Control Population		
Obstructive Sleep Apnea	*Yes*	*No*	P *Value*	*Yes*	*No*	P *Value*
No. of patients (%)	8817 (5.8)	144 421 (94.2)		15 109 (2.0)	731 039 (98.0)	
Gender, % male	76.7	55.2	< 0.001	81.9	55.8	< 0.001
Age (yrs), median (IQR)	63.1 (55.2–69.4)	67.2 (58.2–74.1)	< 0.001	65.9 (58.9–71.5)	66.9 (57.9–73.8)	< 0.001
Duration of diabetes (yrs), median (IQR)*	4.7 (1.6–8.8)	5.4 (2.1–9.8)	< 0.001	N/A	N/A	< 0.001
Marital status, %			< 0.001			< 0.001
Never married	14.1	12.4		8.7	11.5	
Married or living with someone	61.5	59.2		68.6	61.8	
Widowed or divorced	24.4	28.5		22.6	26.7	
Charlson comorbidity index score, %			< 0.001			< 0.001
0 (low)	71.6	77.5		79.7	85.4	
1 (moderate low)	13.8	9.8		7.4	4.8	
2 (moderate high)	9.1	8.7		9.4	7.4	
3 or more (high)	5.6	4.0		3.4	2.4	
Use of medication, %						
Insulin	16.5	15.7	0.058	N/A	N/A	N/A
Glucose-lowering treatment, excluding insulins	89.2	86.4	< 0.001	N/A	N/A	N/A
Antihypertensive drugs	80.7	77.6	< 0.001	5.5	39.5	< 0.001
Cholesterol-lowering drugs	78.6	77.2	0.002	35.8	24.6	< 0.001
Obesity, %	54.5	30.6	< 0.001	18.7	5.8	< 0.001
Level of DR, %			< 0.001			N/A
0	94.0	91.0		N/A	N/A	
1	4.5	6.3		N/A	N/A	
2	0.9	1.8		N/A	N/A	
3	0.2	0.3		N/A	N/A	
4	0.3	0.6		N/A	N/A	

DR = diabetic retinopathy; IQR = interquartile range; N/A = not applicable.
*Duration of diabetes was calculated only for patients with at least 1 International Classification of Diseases, Tenth Revision, code for diabetes or 1 Anatomical Therapeutic Chemical Classification code for treatment of diabetes.

(5.9% vs. 4.2% vs. 3.1% vs. 4.1% vs. 2.9%; $P < 0.001$) for levels 0 through 4, respectively.

Among patients with type 2 diabetes and 746 148 control participants, OSA was diagnosed before the index date in 8817 (5.8%) and 15 109 (2.0%) people, respectively (Table 2). In both groups, patients with OSA were younger and were more likely to be men, to be married, to be registered with obesity, to have a higher Charlson comorbidity index score, and to be treated with antihypertensive and cholesterol lowering drugs. For patients with type 2 diabetes, those with OSA also were more likely to be treated with noninsulin glycemic therapy, but did not differ regarding use of insulin.

Table 3. Odds Ratio with 95% Confidence Interval for Obstructive Sleep Apnea for Patients with Type 2 Diabetes Screened for Diabetic Retinopathy Compared with Age- and Gender-Matched Control Participants According to Level of Diabetic Retinopathy for Patients at the Time of the First Registration in the Danish Registry of Diabetic Retinopathy for Patients

	Patients		Control Participants		Odds Ratio (95% Confidence Interval)		
Level of Diabetic Retinopathy	*With Obstructive Sleep Apnea*	*Without Obstructive Sleep Apnea*	*With Obstructive Sleep Apnea*	*Without Obstructive Sleep Apnea*	*Crude Model*	*Model Adjusted for Gender and Age*	*Multivariable Model**
Overall	8817	144 421	15 109	731 039	2.95 (2.88–3.03)†	2.98 (2.90–3.06)†	2.01 (1.95–2.08)†
Level 0	8291	131 409	13 724	666 583	3.06 (2.98–3.15)†	3.10 (3.01–3.19)†	2.10 (2.03–2.17)†
Levels 1–4	526	13 012	1385	64 456	1.88 (1.70–2.08)†	1.89 (1.70–2.09)†	1.19 (1.05–1.34)†
Level 1	400	9095	954	45 188	2.08 (1.85–2.35)†	2.09 (1.86–2.36)†	1.36 (1.19–1.57)†
Level 2	82	2600	291	12 768	1.38 (1.08–1.77)†	1.39 (1.08–1.78)†	0.88 (0.61–1.07)
Level 3	17	402	48	2006	1.77 (1.01–3.10)†	1.77 (1.01–3.12)†	0.79 (0.41–1.54)
Level 4	27	915	92	4494	1.44 (0.93–2.23)	1.44 (0.93–2.23)	0.93 (0.56–1.57)

*Multivariable logistic regression model adjusted for gender, age, marital status, use of antihypertensive drugs, cholesterol-lowering drugs, and Charlson comorbidity index.
†Statistically significant.

Table 4. Odds Ratio with 95% Confidence Interval for Obstructive Sleep Apnea for Patients Screened for Diabetic Retinopathy at the Time of the Index Date* According to Level of Diabetic Retinopathy (Level 0 Used as Reference)

Level of Diabetic Retinopathy	People with Obstructive Sleep Apnea	People without Obstructive Sleep Apnea	Odds Ratio (95% Confidence Interval)		
			Crude Model	*Model Adjusted for Gender and Age*	*Multivariable Model*†
Level 0	8817	144 421	1 (Reference)	1 (Reference)	1 (Reference)
Level 1-4	526	13 012	0.64 (0.59–0.70)‡	0.59 (0.54–0.65)‡	0.57 (0.52–0.62)‡
Level 1	400	9095	0.70 (0.63–0.77)‡	0.66 (0.60–0.73)‡	0.64 (0.58–0.71)‡
Level 2	82	2600	0.50 (0.40–0.62)‡	0.44 (0.35–0.55)‡	0.42 (0.34–0.53)‡
Level 3	17	402	0.67 (0.41–1.09)	0.51 (0.31–0.84)‡	0.48 (0.29–0.78)‡
Level 4	27	915	0.47 (0.32–0.69)‡	0.43 (0.30–0.64)‡	0.40 (0.27–0.59)‡

*Index date defined as the date of the first registration in the Danish Registry of Diabetic Retinopathy for patients.
†Multivariable logistic regression model adjusted for gender, age, marital status, use of antihypertensive drugs, cholesterol-lowering drugs, and Charlson comorbidity index.
‡Statistically significant.

As compared with control participants, a higher presence of OSA was found for the entire group of patients with type 2 diabetes (multivariable adjusted OR, 2.01; 95% CI, 1.95–2.08; Table 3). The higher levels of OSA in patients were identified both in those without DR (multivariable adjusted OR, 2.10; 95% CI, 2.03–2.17) and with DR (multivariable adjusted OR, 1.19; 95% CI, 1.05–1.34). In analyses stratified for obesity (data not shown), the excess risk of OSA was demonstrated in patients without a diagnosis of obesity (OR, 1.32; 95% CI, 1.26–1.37), as well as in those with obesity (OR, 3.87; 95% CI, 3.67–4.09).

When patients without DR were used as references, patients with DR (levels 1–4 combined) were less likely to have OSA at the index date (multivariable adjusted OR, 0.57; 95% CI, 0.52–0.62), and this was confirmed for all levels of DR between 1 and 4 (multivariable adjusted OR, 0.64 vs. 0.42 vs. 0.48 vs. 0.40; Table 4). Consistent findings were identified in analyses stratified for obesity (multivariable adjusted OR for DR levels 1–4 combined, 0.46 [95% CI, 0.39–0.54] and 0.54 [95% CI, 0.48–0.60] for patients without and with obesity, respectively).

A higher 5-year incidence of OSA was identified in patients as compared to control participants (Table 5). Including all persons, 2262 and 4897 events of incident OSA were identified in 436 021 and 2 192 653 years of risk in patients and control participants, respectively (multivariable adjusted HR, 1.55; 95% CI, 1.46–1.64; Table 5). The competing risk analysis resulted in estimates consistent with the main analysis (multivariable adjusted HR, 1.52; 95% CI, 1.43–1.62, data not shown). This excess risk of incident OSA was identified both in patients without DR (multivariable adjusted HR, 1.56; 95% CI, 1.47–1.66) and with DR (multivariable adjusted HR, 1.42; 95% 1.16–1.73). In the model stratified for obesity, the excess risk of incident OSA was identified only in patients with obesity (multivariable adjusted HR, 2.80; 95% CI, 2.55–3.08, data not shown).

Defining patients with type 2 diabetes but without DR as references, those with DR (levels 1–4 combined) at baseline showed a lower risk of OSA developing within 5 years (multivariable adjusted HR, 0.86; 95% CI, 0.74–0.99; Table 6), and these findings were confirmed in both

Table 5. Hazard Ratio with 95% Confidence Interval for Incident Obstructive Sleep Apnea after the Index Date* for Patients with Type 2 Diabetes Screened for Diabetic Retinopathy and Age- and Gender-Matched Control Participants According to Level of Diabetic Retinopathy for Patients

Level of Diabetic Retinopathy	Patients		Controls		Hazard Ratio (95% Confidence Interval)		
	Events of Sleep Apnea†	*Years of Risk*	*Events of Sleep Apnea*†	*Years of Risk*	*Crude Model*	*Model Adjusted for Gender and Age*	*Multivariable Model*‡
Overall	2262	436 021	4897	2 192 653	2.32 (2.21–2.44)§	2.36 (2.25–2.48)§	1.55 (1.46–1.64)§
Level 0	2051	392 990	4436	1 977 652	2.33 (2.21–2.45)§	2.37 (2.25–2.50)§	1.56 (1.47–1.66)§
Level 1–4	211	43 031	461	215 002	2.29 (1.94–2.69)§	2.31 (1.96–2.72)§	1.42 (1.16–1.73)§
Level 1	144	30 018	310	149 677	2.32 (1.90–2.82)§	2.34 (1.92–2.86)§	1.42 (1.12–1.80)§
Level 2	44	8658	105	43 457	2.11 (1.48–3.00)§	2.11 (1.48–3.00)§	1.27 (0.83–1.95)
Level 3	5	1274	17	6500	1.50 (0.55–4.07)	1.51 (0.56–4.09)	1.74 (0.50–6.07)
Level 4	18	3082	29	15 368	3.09 (1.72–5.57)§	3.11 (1.73–5.61)§	1.76 (0.82–3.75)

*Index date defined as the date of the first registration in the Danish Registry of Diabetic Retinopathy for patients.
†Given as the number of patients with new registration of sleep apnea after the index date.
‡Cox regression model adjusted for gender, age, marital status, use of antihypertensive drugs, cholesterol-lowering drugs, and Charlson comorbidity index.
§Statistically significant.

Table 6. Hazard Ratio with 95% Confidence Interval for Incident Obstructive Sleep Apnea after the Index Date* for Patients with Type 2 Diabetes Screened for Diabetic Retinopathy According to Level of Diabetic Retinopathy (Level 0 Used as Reference)

Level of Diabetic Retinopathy	Events of Obstructive Sleep Apnea†	Years of Risk	Hazard Ratio (95% Confidence Interval)		
			Crude model	*Model Adjusted for Gender and Age*	*Multivariable Model‡*
Level 0	2051	392 990	1 (Reference)	1 (Reference)	1 (Reference)
Level 1–4	211	43 031	0.94 (0.82–1.09)	0.88 (0.77–1.02)	0.86 (0.74–0.99)§
Level 1	144	30 018	0.92 (0.78–1.09)	0.89 (0.75–1.06)	0.88 (0.75–1.05)
Level 2	44	8658	0.98 (0.73–1.32)	0.86 (0.63–1.15)	0.81 (0.60–1.10)
Level 3	5	1274	0.76 (0.31–1.82)	0.56 (0.23–1.34)	0.53 (0.22–1.28)
Level 4	18	3082	1.13 (0.71–1.79)	1.09 (0.69–1.73)	0.96 (0.59–1.54)

*Index date defined as the date of the first registration in the Danish Registry of Diabetic Retinopathy for patients.
†Given as the number of patients with new registration of obstructive sleep apnea after the index date.
‡Cox regression model adjusted for gender, age, marital status, use of antihypertensive drugs, cholesterol-lowering drugs, and Charlson comorbidity index.
§Statistically significant.

stratification models for obesity (multivariable adjusted HR, 0.71 [95% CI, 0.54–0.93] and 0.78 [95% CI, 0.66–0.93] for patients without and with obesity, respectively; data not shown).

Finally, among 95 580 patients without DR at the index date, 7706 (8.1%) demonstrated DR in either eye within 5 years. In this group, the lowest risk of incident DR was demonstrated for those with OSA at baseline (multivariable adjusted HR, 0.83; 95% CI, 0.74–0.92; Table 7).

Discussion

In this registry-based cohort study, we evaluated the risk of present and incident OSA in a national cohort of 900 000 patients with type 2 diabetes and nondiabetic control participants matched for age and gender. In multivariable adjusted models, patients with type 2 diabetes had a 2.01 and 1.55 times higher risk of present and incident OSA, respectively. Surprisingly, patients with DR independently were less likely to have OSA at the time of the index date and to demonstrate OSA through 5 years of observation, which included 2.5 million years of risk time for patients and control participants combined.

In a systematic review, Leong et al[10] reported positive associations between DR and OSA in 11 of 15 studies, including a total of 2731 patients, but given the heterogeneity between studies, it was not possible to evaluate the effect size in a meta-analysis. In our study, patients screened for DR for the first time showed twice the prevalence of OSA as age- and gender-matched persons without diabetes. Unexpectedly, the highest risk was identified in patients without DR, who, independently of other factors, had a 14% and 43% higher rate of prevalent and incident OSA, respectively, as compared with patients with DR. With the data at hand, we cannot know if this can be explained by pathophysiologic mechanisms or if this was a result of a potentially better awareness of diabetes and associated complications in those without DR, which could make these patients more likely to receive a hospital-based diagnosis for OSA.

As far as we know, the longitudinal association between OSA and DR has been examined only by Altaf et al.[16] In 5 years, patients with OSA showed a higher risk of progression to preproliferative DR or proliferative DR as compared with patients without OSA (18.4% vs. 6.11%; $P = 0.02$). This may be explained by hypoxia-induced retinal damage, given that the retina is more vulnerable for hypoxic damage during night hours.[30] In our study, we independently demonstrated a 17% lower 5-year risk of DR for those with OSA at the time of the first DR screening. Although both studies evaluated 5-year outcomes in patients with type 2 diabetes, the different results may be explained by different study populations and clinical outcomes.

Table 7. Hazard Ratio with 95% Confidence Interval for Diabetic Retinopathy Developing in at Least 1 Eye According to Occurrence of Obstructive Sleep Apnea at the Time of the Index Date* in the Danish Registry of Diabetic Retinopathy

	Obstructive Sleep Apnea		No Obstructive Sleep Apnea		Hazard Ratio (95% Confidence Interval)		
	Events†	*Person-Years*	*Events†*	*Person-Years*	*Crude Model*	*Model Adjusted for Gender and Age*	*Multivariable Model‡*
Incident DR	371	18 308	7335	314 459	0.87 (0.78–0.97)§	0.85 (0.77–0.95)§	0.83 (0.74–0.92)§

DR = diabetic retinopathy.
*Index date defined as the date of the first registration in the Danish Registry of Diabetic Retinopathy.
†Given as the number of patients with a new registration of DR levels 1–4 (according to the International Clinical Retinopathy Disease Severity Scale) in at least 1 eye level after the index date.
‡Cox regression model adjusted for gender, age, marital status, use of antihypertensive drugs, cholesterol-lowering drugs, and Charlson comorbidity index.
§Statistically significant.

Although the study by Altaf et al evaluated late-stage progression to sight-threatening DR in 230 patients, we demonstrated that OSA independently acted as a marker of progression for the onset of DR in a national cohort of almost 100 000 patients. Although we would not expect OSA to be a causal protector of DR from a pathophysiologic point of view, our results could indicate that patients with OSA might have obtained a better understanding of diabetic complications and measurements for avoidance, like improved glycemic control, blood pressure lowering, and better management of dyslipidemia.

In our study, we also tested the reverse hypothesis that DR could predict OSA. The notion that sleep disorders could be a consequence of DR was proposed by Tan et al,[31] who pointed out that neurodegeneration of melanopsin-expressing retinal ganglion cells[32] and nighttime melatonin depression[33] may cause disruption of the circadian rhythm. This is clinically important, given the possibility of including OSA screening in diabetes-related screening programs. However, although we reported that patients with type 2 diabetes independently were more likely to have and to go on to demonstrate OSA, our data indicate that DR is more likely to act as a marker of protection and that the excess risk of OSA developing is more likely to be explained by other factors associated with diabetes, although our data could not demonstrate that obesity was a defining factor.[11]

Among the strengths of the study, we were able to include a full national cohort of patients attending diabetic eye screening, and each of these specifically was matched by 5 persons of the same age and gender without diabetes. Also, we had information regarding levels of DR as well as systemic comorbidity and medication, as given by a variety of validated national registers. Finally, we were able to perform a longitudinal evaluation of DR as a marker of incident OSA, including more than 2.5 million years of time of risk.

Limitations of the study are important to acknowledge. In general, register-based studies are always subject to potential inaccuracies in coding practice, and some factors (i.e., obesity) may be underreported in registers. Likewise, although we were able to control for type and duration of diabetes, obesity, use of insulin, noninsulin glucose-lowering drugs, antihypertensive drugs, and body mass index, we were not able to account for severity of OSA, glycemic regulation blood pressure measurements, and smoking because these data were not available in the registers.

In conclusion, in the present nationwide study of approximately 900 000 people, patients with type 2 diabetes were twice as likely to have OSA, with the highest risk identified in those without DR. Patients with type 2 diabetes also were more than 50% as likely to demonstrate OSA within 5 years, but DR and OSA were linked inversely with a lower risk for each other.

Footnotes and Disclosures

Originally received: February 18, 2021.
Final revision: March 5, 2021.
Accepted: March 8, 2021.
Available online: March 12, 2021. Manuscript no. D-21-00020.

[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] Open Patient Data Explorative Network, Odense University Hospital & University of Southern Denmark, Odense, Denmark.

[5] Department of Ophthalmology, Zealand University Hospital Roskilde, Roskilde, Denmark.

[6] Organization of Danish Practicing Ophthalmologists, Copenhagen, Denmark.

[7] Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark.

[8] Department of Ophthalmology, Rigshospitalet-Glostrup, Copenhagen, Denmark.

[9] Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.

[10] Department of Vision Informatics, University of Osaka, Osaka, Japan.

[11] Department of Ophthalmology, Aalborg University Hospital, Aalborg, Denmark.

Disclosure(s):
All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s): R.K.: Financial support (to institution) — Topcon, Senju, Novartis

Supported by Velux Fonden (grant no.: 00028744). The funding organization had no role in the design or conduct of this research.

HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees at Region of Southern Denmark and the Danish Clinical Registries approved the study. All research adhered to the tenets of the Declaration of Helsinki. According to Danish law, informed consent and permissions from the Danish National Committee on Health Research Ethics are not required for register-based studies.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Grauslund, Stokholm, Thykjær, Möller, Laugesen, Andresen, Bek, la Cour, Heegaard, Højlund, Kawasaki, Hajari, Kyvik, Schielke, Rubin, Rasmussen

Analysis and interpretation: Grauslund, Stokholm, Thykjær, Möller, Laugesen, Andresen, Bek, la Cour, Heegaard, Højlund, Kawasaki, Hajari, Kyvik, Schielke, Rubin, Rasmussen

Data collection: Grauslund, Stokholm, Thykjær, Möller, Laugesen, Andresen, Bek, la Cour, Heegaard, Højlund, Kawasaki, Hajari, Kyvik, Schielke, Rubin, Rasmussen

Obtained funding: For all authors, the study was performed as part of regular employment duties. No additional funding was provided.

Overall responsibility: Grauslund, Stokholm, Thykjær, Möller, Laugesen, Andresen, Bek, la Cour, Heegaard, Højlund, Kawasaki, Hajari, Kyvik, Schielke, Rubin, Rasmussen

Abbreviations and Acronyms:
CI = confidence interval; **DiaBase** = Danish Registry of Diabetic Retinopathy; **DR** = diabetic retinopathy; **HR** = hazard ratio; **ICD** = International Classification of Diseases; **OR** = odds ratio; **OSA** = obstructive sleep apnea.

Keywords:
diabetic retinopathy, obstructive sleep apnea, type 2 diabetes, screening, epidemiology.

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

References

1. Grauslund J, Green A, Sjolie AK. Prevalence and 25 year incidence of proliferative retinopathy among Danish type 1 diabetic patients. *Diabetologia*. 2009;52(9):1829−1835.
2. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. *Ophthalmology*. 2008;115(11):1859−1868.
3. Klein R, Lee KE, Gangnon RE, Klein BE. The 25-year incidence of visual impairment in type 1 diabetes mellitus: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Ophthalmology*. 2010;117(1):63−70.
4. Grauslund J, Green A, Sjolie AK. Blindness in a 25-year follow-up of a population-based cohort of Danish type 1 diabetic patients. *Ophthalmology*. 2009;116(11):2170−2174.
5. Stefansson E, Bek T, Porta M, et al. Screening and prevention of diabetic blindness. *Acta Ophthalmol Scand*. 2000;78(4):374−385.
6. DCCT/EDIC Research Group, Nathan DM, Bebu I, et al. Frequency of evidence-based screening for retinopathy in type 1 diabetes. *N Engl J Med*. 2017;376(16):1507−1516.
7. Grauslund J, Andersen N, Andresen J, et al. Evidence-based Danish guidelines for screening of diabetic retinopathy. *Acta Ophthalmol*. 2018;96(8):763−769.
8. Scanlon PH. The English National Screening Programme for diabetic retinopathy 2003−2016. *Acta Diabetol*. 2017;54(6):515−525.
9. Wang LZ, Cheung CY, Tapp RJ, et al. Availability and variability in guidelines on diabetic retinopathy screening in Asian countries. *Br J Ophthalmol*. 2017;101(10):1352−1360.
10. Leong WB, Jadhakhan F, Taheri S, et al. Effect of obstructive sleep apnoea on diabetic retinopathy and maculopathy: a systematic review and meta-analysis. *Diabet Med*. 2016;33(2):158−168.
11. Qie R, Zhang D, Liu L, et al. Obstructive sleep apnea and risk of type 2 diabetes mellitus: a systematic review and dose-response meta-analysis of cohort studies. *J Diabetes*. 2020;12(6):455−464.
12. Siwasaranond N, Nimitphong H, Manodpitipong A, et al. The relationship between diabetes-related complications and obstructive sleep apnea in type 2 diabetes. *J Diabetes Res*. 2018;2018:9269170.
13. Schulz R, Hummel C, Heinemann S, et al. Serum levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea and severe nighttime hypoxia. *Am J Respir Crit Care Med*. 2002;165(1):67−70.
14. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med*. 1994;331(22):1480−1487.
15. Shiba T, Takahashi M, Matsumoto T, Hori Y. Sleep-disordered breathing is a stronger risk factor for proliferative diabetic retinopathy than metabolic syndrome and the number of its individual components. *Semin Ophthalmol*. 2019;34(2):59−65.
16. Altaf QA, Dodson P, Ali A, et al. Obstructive sleep apnea and retinopathy in patients with type 2 diabetes. A longitudinal study. *Am J Respir Crit Care Med*. 2017;196(7):892−900.
17. Sankar A, Dixon PR, Sivanathan L, et al. Cost-effectiveness analysis of preoperative screening strategies for obstructive sleep apnea among patients undergoing elective inpatient surgery. *Anesthesiology*. 2020;133(4):787−800.
18. Wilkinson CP, Ferris FL, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*. 2003;110(9):1677−1682.
19. Andersen N, Hjortdal JO, Schielke KC, et al. The Danish Registry of Diabetic Retinopathy. *Clin Epidemiol*. 2016;8:613−619.
20. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541−549.
21. World Health Organization. International Classification of Diseases. http://www.who.int/classifications/icd/en/. Accessed 21.10.18.
22. Schmidt M, Schmidt SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449−490.
23. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676−682.
24. Brusselaers N, Lagergren J. The Charlson comorbidity index in registry-based research. *Methods Inf Med*. 2017;56(5):401−406.
25. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7 Suppl):38−41.
26. World Health Organization. Anatomical therapeutic chemical (ATC) classification. 01.02.2019. Available at: https://www.who.int/medicines/regulation/medicines-safety/toolkit_atc/en/. Accessed 01.03.19.
27. Nordic Medico-Statistical Committee (NOMESCO). NOMESCO classification of surgical procedures (NCSP), version 1.16. Available at: http://www.nordclass.se/NCSP_1_16.pdf. Accessed 12.06.19.
28. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496−509.
29. Grauslund J, Stokholm L, Ohm Kyvik K, et al. Interactions between ocular and systemic disease using national register-based data in the Danish Excellence Centre in Ophthalmic Epidemiology (DECODE-EYE): study perspective. *Acta Ophthalmol*. 2020;98(6):573−578.
30. Drasdo N, Chiti Z, Owens DR, North RV. Effect of darkness on inner retinal hypoxia in diabetes. *Lancet*. 2002;359(9325):2251−2253.

31. Tan NYQ, Chew M, Tham YC, et al. Associations between sleep duration, sleep quality and diabetic retinopathy. *PLoS One*. 2018;13(5):e0196399.
32. Obara EA, Hannibal J, Heegaard S, Fahrenkrug J. Loss of melanopsin-expressing retinal ganglion cells in patients with diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2017;58(4): 2187−2192.
33. Hikichi T, Tateda N, Miura T. Alteration of melatonin secretion in patients with type 2 diabetes and proliferative diabetic retinopathy. *Clin Ophthalmol*. 2011;5:655−660.