Longitudinal bidirectional associations between diabetic retinopathy and diagnosed depression

Results from a Danish nationwide registry-based cohort study

Pedersen, Frederik N.; Stokholm, Lonny; Andersen, Nis; Andresen, Jens; Bek, Toke; Hajari, Javad N.; Heegaard, Steffen; Højlund, Kurt; Kawasaki, Ryo; Möller, Sören; Laugesen, Caroline S.; Schielke, Katja C.; Thykjær, Anne S.; Peto, Tunde; Pouwer, Frans; Grauslund, Jakob

Published in:
Journal of Diabetes and its Complications

DOI (link to publication from Publisher):
10.1016/j.jdiacomp.2023.108589

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

Journal of Diabetes and Its Complications 37 (2023) 108589

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: www.elsevier.com/locate/jdiacomp

Longitudinal bidirectional associations between diabetic retinopathy and diagnosed depression: Results from a Danish nationwide registry-based cohort study

Frederik N. Pedersen [a,b,*], Lonny Stokholm [b,c], Nis Andersen [d], Jens Andresen [d], Toke Bek [e], Javad N. Hajari [f], Steffen Heegaard [f,g], Kurt Højlund [b,h], Ryo Kawasaki [b,i], Sören Möller [b,c], Caroline S. Laugesen [j], Katja C. Schielke [k], Anne S. Thykjær [a,b,h], Tunde Peto [b,l], Frans Pouwer [h,m,n], Jakob Grauslund [a,b,h]

[a] Department of Ophthalmology, Odense University Hospital, Odense, Denmark
[b] Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[c] OPEN – Open Patient data Explorative Network, Odense University Hospital & University of Southern Denmark, Odense, Denmark
[d] Organization of Danish Practicing Ophthalmologists, Copenhagen, Denmark
[e] Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark
[f] Department of Ophthalmology, Rigshospitalet-Glostrup, Copenhagen, Denmark
[g] Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[h] Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark
[i] Department of Vision Informatics, University of Osaka, Osaka, Japan
[j] Department of Ophthalmology, Zealand University Hospital Roskilde, Roskilde, Denmark
[k] Department of Ophthalmology, Aalborg University Hospital, Aalborg, Denmark
[l] School of Medicine, Dentistry and Biomedical Sciences, Queen's University, Belfast, Northern Ireland, United Kingdom
[m] Department of Psychology, University of Southern Denmark, Odense, Denmark
[n] Department of Medical Psychology, Amsterdam UMC, Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
Depression
Diabetic retinopathy
Type 2 diabetes
Diabetes
Mood disorder
Epidemiology

ABSTRACT

Objective: Diabetic retinopathy (DR) is a feared complication and a leading course of visual impairment, but the connection between DR and depression including the direction has never been studied in a nationwide cohort. We aimed to assess, whether the associations between DR and diagnosed depression are bidirectional.

Methods: We performed a national register-based cohort study of individuals with type 2 diabetes, who attended diabetic eye screening between January 2013 and June 2022. Level of DR was extracted from the Danish Registry of Diabetic Retinopathy. The severity of DR was assessed according to the International Clinical Diabetic Retinopathy severity scale. Diagnosed depression was ascertained by physician diagnostic codes of unipolar depression (F32), recurrent depression (F33) or dysthymia (F34.1) from the Danish National Patient Register. We estimated presence of diagnosed depression according to DR level at index date and risk of diagnosed depression during follow-up using multivariable logistic and Cox regression, respectively. Secondly, we assessed whether diagnosed depression at index date could predict incident DR.

Results: We included 240,893 individuals with type 2 diabetes with baseline rates of diagnosed depression ranging from 5.2 to 6.0 % for DR level 1–4. At index date, individuals with type 2 diabetes and DR were less likely to have a history of diagnosed depression (multivariable adjusted OR, 0.77 [95 % CI 0.73–0.82]). In 226,523 individuals with type 2 diabetes followed for 1,159,755 person-years, 1.7 % developed at least one episode of diagnosed depression.

In a model adjusted for age and sex, individuals with DR at index date had an increased risk of incident diagnosed depression compared to those without DR (HR 1.25 [95 % CI 1.16–1.36]). Adjusting for marital status, use of glucose-, lipid- and blood pressure lowering medication, HbA1c, diabetic neuropathy and Charlson comorbidity index waived the above risk (multivariable adjusted HR 1.02 [95 % CI 0.93–1.12]).

* Corresponding author at: Department of Ophthalmology, Odense University Hospital, J. B. Winsløws Vej 4, 5000 Odense C, Denmark.
E-mail address: Frederik.norregaard.pedersen@rsyd.dk (F.N. Pedersen).

https://doi.org/10.1016/j.jdiacomp.2023.108589
Received 23 April 2023; Received in revised form 31 July 2023; Accepted 19 August 2023
Available online 24 August 2023

Furthermore a previous history of diagnosed depression was not associated with increased risk of incident DR (multivariable adjusted HR 0.89 [95 % CI 0.77–1.03]).
Conclusion: In this nationwide cohort study, individuals with DR at first screening were 23 % less likely to have a history of depression, but our data did not support a bidirectional association between DR and depression. Selection bias may have occurred as diagnosed depression is a known barrier for attending DR-screening.

1. Introduction

Individuals with type 2 diabetes are twice as likely to develop depression compared to the general population.[1] Depression in people with diabetes often leads to suboptimal HbA_{1c} levels,[2] impaired quality of life,[3] and higher mortality.[4] Diabetic retinopathy (DR) is the most common complication in diabetes and leading course of blindness in those with diabetes.[5,6] An association between DR and depression has been proposed to be explainable by both behavioral and biological factors. Depression can contribute to impaired self-care behaviors including a less healthy diet, lower levels of exercise, and less optimal glucose self-management, that can subsequently result in higher HbA_{1c} levels and increased risk of incident and progression of DR.[7] Vice versa, DR may also be associated with the development of depression through fear of functional limitations due to vision loss.[8] A German study found that individuals with type 2 diabetes and DR had a 44 % increased risk of developing depression during 10 years of follow-up.[9] To our knowledge, only one prospective study has investigated the risk of incident DR in people with type 2 diabetes and depression.[10] The study reported a slightly elevated risk of 2.5 % but was overall limited by a small sample size. From a clinical point of view, it is important to establish whether DR in type 2 diabetes can be a predictive marker of depression and vice versa in order to provide optimal preventive healthcare. Although we have some prior knowledge describing the association this has most often been obtained in smaller cross sectional studies.[11] We will add data from a long-term longitudinal study of a nationwide cohort of individuals with type 2 diabetes attending the Danish national DR screening program to investigate the bidirectional association of DR and diagnosed depression.

2. Material and methods

2.1. Data sources

For the present study, five Danish national data sources were utilized; 1) The Danish Registry of Diabetic Retinopathy (DiaBase) has collected data since 2013 for all individuals above the age of 18 years attending the DR screening program in Denmark.[12] The screening program is tax-funded and performed by practicing ophthalmologists or at selected hospitals. It is mandatory to report findings, which include but is not limited to level of DR, visual acuity and prior eye surgery. The screening procedure is primarily based on retinal fundus images according to national guidelines.[13] Level of DR is reported according to International Clinical Diabetic Retinopathy Disease Severity Scale, which contains five stages: level 0 (no DR), levels 1–3 (mild, moderate and severe DR) and level 4 (proliferative DR).[14] 2) The Danish National Patient Registry (DNPR) was established in 1977 and holds, on an individualized basis, information on all hospital contacts, including hospitalization and outpatient visits, e.g. admission date and medical diagnosis, as given by International Classification of Disease 10th (ICD-10) codes.[15] 3) The Danish National Prescription Registry contains all dispensed prescriptions issued by general practitioners or specialists since 1995, in accordance with the Anatomical Therapeutic Chemical Classification (ATC) system.[16,17] 4) The Register of Laboratory Results for Research contains, on an individualized level, routine biomarker results analyzed in public hospital laboratories, including samples from general practitioners.[18] 5) The Danish Civil Registration System registers each Danish citizen with a unique personal identification number, which was used to link data between the above registries. Furthermore, this registry holds information on date of birth, sex, marital and vital status.[19]

2.2. Study population

We performed a Danish nationwide register-based cohort study of individuals registered in DiaBase defined with type 2 diabetes between 1 January 2013 and 1 June 2022. The first eye screening registered in Diabase defined the index date. Level of DR was defined according to level of DR at the worse eye. As all individuals in DiaBase have diabetes, we excluded those with type 1 diabetes defined from four criteria by combining ICD-10 codes for diabetes and ATC codes of redeemed prescription of insulin (A10A*) and oral glucose lowering drugs excl. Insulin (A10B*). The definition of type 1 diabetes was 1) latest given diagnostic code in DNPR must be E10*, and 2) first prescription of A10A within a year of first E10 diagnosis, and 3) last prescription of A10A within a year of end of follow-up, and number of prescriptions $\geq$ number of years from first prescription to end of follow-up. Diagnosed depression was defined by any of the first registered ICD-10 codes F32 (depressive episode), F33 (recurrent depressive disorder), or F34.1 (dysthymia) as in- or outpatient visits.

2.3. Study outcomes

Our primary outcome was risk of a previous registration of diagnosed depression before the index date according to DR level 0–4. As a secondary outcome, we assessed the risk of incident diagnosed depression according to DR level 0–4 during follow-up. Time of risk was calculated as the time between index date and date of the first registration of diagnosed depression, death, migration or end of follow-up at 1 June 2022, whichever came first. Lastly, our third outcome was risk of incident DR according to a previous registration of diagnosed depression or not. At index date, individuals with type 2 diabetes without DR, with and without diagnosed depression were followed. DR incidence was defined by a progression from DR level 0 to DR level 1 or higher in at least one eye during follow-up.

2.4. Covariate assessments

Comorbidities were assessed by the Charlson comorbidity index score calculated from ICD-10, as given by Quan et al.[20] Diabetic neuropathy was assessed by ICD-10 codes (G590, G332 or E114). Use of medication was assessed by ATC-codes for insulin (A10A*), oral glucose lowering drugs (A10B*), antihypertensive treatment (C03*, C07*, C08*, C09*) or lipid lowering therapy (C10*), as prescribed minimum twice within one year prior of index date. Duration of diabetes was given by the difference between the first date of ICD-10 codes for diabetes or date of redeemed prescription of insulin or glucose lowering drugs excl. Insulin and index date. Marital status at index date was retrieved from the Danish Civil Registration System register and reported as never married, married or widowed/divorced. Level of HbA_{1c} was calculated as the mean value of measurements performed within one calendar year, prior to or after, index date.

2.5. Statistical analyses

Continuous variables are presented with mean and interquartile

range and categorical variables with frequencies and percentages. We applied Cuzick's extension of the Wilcoxon rank-sum test for trends for several groups and Pearson chi-squared test (χ^2) to test differences between groups (Table 1 and Table 2). In the cross-sectional analysis (Table 3), we calculated odds ratios (OR) with 95 % confidence intervals (CI) for diagnosed depression in a crude, age- and sex-adjusted, and multivariable logistic regression model (adjusted for age, sex, marital status, glucose-, lipid- or blood pressure lowering medication, HbA1c, diabetic neuropathy and an adjusted Charlson comorbidity index. As a sensitivity analysis, we restricted the diagnosis of diagnosed depression to have been given within two year before index date (Supplementary material Table S1).

In the prospective analysis, we calculated hazards ratios (HR) for diagnosed depression (Table 4) in a crude, age- and sex-adjusted and a multivariable Cox regression model (we used the same confounding variables as for the multivariable logistic regression model). We utilized DR as a time-varying exposure meaning that individuals contributed to risk time depending on the DR level, which could change based on their screening results during follow-up. Civil status, use of medication and CCI were used as time-varying covariates. As a sensitivity analysis, risk of incident diagnosed depression was investigated without the time-varying aspect, meaning that the first DR screening result was used a predictor of incident diagnosed depression (Supplementary material Table S2).

Lastly, we investigated the reverse association estimating the risk of incident DR with diagnosed depression as the predictor (Table 5). This analysis was performed among individuals with at least two screening episodes and no DR at index date. In a sensitivity analysis, we restricted codes for diagnosed depression to be given within one and two year of the first reported DR screening. The proportional hazard assumption was checked visually in log–log and Schoenfeld residual plots. We tested for interaction and found none between age and sex. We had 6.0 % and 6.8 % missing values in HbA_{1c} and diabetes duration, respectively. Missing data were considered missing at random, and due to the relative small proportion of missing data, we did not perform any statistical corrections. CI that did not include 1.0 and *p*-values below 0.05 were considered statistically significant. All statistics were performed using

Table 2
Characteristic of individuals with type 2 diabetes with and without diagnosed depression at the time of the first registration in the Danish Registry of Diabetic Retinopathy.

	Individuals with diagnosed depression	Individuals without diagnosed depression	*p*-Value
Number of patients, n	14,370	226,523	
Sex, % male	43.8	57.7	<0.001
Age, years, median (IQR)	60.5 (51.6;69.9)	66.3 (56.9;73.5)	<0.001
Duration of diabetes, years, median (IQR)[a]	5.7 (1.6;11.4)	5.7 (1.7;11.5)	0.485
Marital status, %			<0.001
Never married	20.9	14.3	
Married	43.1	58.2	
Widowed or divorced	36.0	27.5	
Charlson Comorbidity Index score, %			<0.001
0 (low)	58.4	66.5	
1 (moderate low)	18.1	14.8	
2 (Moderate high)	12.6	11.5	
≥3 (high)	10.9	7.2	
Diabetic neuropathy, %	5.5	4.1	<0.001
Use of medication, %			
Insulin	25.8	21.6	<0.001
Glucose lowering treatment, excl. insulins	79.5	79.9	0.224
Antihypertensive drugs	71.6	77.1	<0.001
Cholesterol lowering drugs	69.9	70.8	0.021
Level of DR, %			0.004
0	87.6	86.6	
	7.6	8.2	
2	2.5	2.8	
3	0.4	0.5	
4	1.9	1.9	
HbA_{1c}, mmol/mol (IQR)	51.3 (45.8;62.2)	51.3 (46.0;60.8)	0.995
HbA_{1c}, % (IQR)	6.8 (6.3;7.8)	6.8 (6.4;7.7)	0.995

DR: diabetic retinopathy; IQR: interquartile range.
[a] Duration of diabetes was calculated only in individuals with at least one International Classification of Disease, Tenth Revision, code for diabetes or one Anatomical Therapeutic Chemical Classification code for treatment of diabetes.

Table 1
Characteristics for individuals with Type 2 Diabetes at the first time of screening for diabetes retinopathy according to the level of diabetic retinopathy as given by the Danish Registry of Diabetic Retinopathy.

	Overall	Level of diabetic retinopathy					*p*-Value
		Level 0	Level 1	Level 2	Level 3	Level 4	
Number of patients, n	240,893	208,772	19,705	6777	1123	4516	
Sex, % male	56.9	56.2	59.9	63.5	68.7	59.7	<0.001
Age, years (IQR)	66.0 (56.6;73.4)	66.2 (57.0;73.5)	65.3 (54.9;73.2)	63.1 (53.6;71.3)	57.7 (48.8;66.6)	62.8 (51.8;71.3)	<0.001
Duration of diabetes, years (IQR)[a]	5.7(1.7;11.5)	4.8(1.4;9.7)	14.0(7.3;19.2)	14.2(7.5;19.0)	14.9(8.4;19.1)	19.5(16.0;21.5)	<0.001
Marital status, %							<0.001
Never married	14.7	14.1	16.9	19.5	25.4	21.4	
Married or living with someone	57.3	57.7	55.3	53.2	48.9	52.7	
Widowed or divorced	28.0	28.1	27.7	27.3	25.7	25.9	
Charlson Comorbidity Index score, %							<0.001
0 (low)	66.0	69.3	49.8	45.3	42.2	21.6	
1 (moderate low)	15.0	12.4	28.1	31.5	37.1	48.6	
2 (Moderate high)	11.5	11.5	11.0	11.2	10.7	14.7	
≥3 (high)	7.4	6.7	11.1	12.0	10.0	15.1	
Use of medication, %							<0.001
Insulin	21.8	15.8	54.9	63.1	67.2	81.3	<0.001
Glucose lowering treatment, excl. insulins	79.9	82.1	69.0	71.1	67.7	42.2	<0.001
Antihypertensive drugs	76.8	76.3	79.2	77.9	72.9	86.6	<0.001
Cholesterol lowering drugs	70.7	70.8	70.9	68.2	61.9	72.0	0.023
Diabetic neuropathy	4.2	3.0	10.3	11.3	12.6	15.7	<0.001
Depression, %	6.0	6.0	5.5	5.2	5.6	6.0	0.013
HbA1c mmol/mol (IQR)	51.3 (46.0;61.0)	50.5 (45.8;58.8)	59.0 (50.5;69.2)	63.8 (54.0;75.5)	68.2 (58.0;80.7)	63.0 (54.2;73.0)	<0.001
HbA1c % (IQR)	6.8 (6.4;7.7)	6.8 (6.3;7.5)	7.5 (6.8;8.5)	8.0 (7.1;9.1)	8.4 (7.5;9.5)	7.9 (7.1;8.8)	<0.001

IQR: interquartile range.
[a] Duration of diabetes was calculated only in individuals with at least one International Classification of Disease, Tenth Revision, code for diabetes or one Anatomical Therapeutic Chemical Classification code for treatment of diabetes.

Table 3
Odds ratio (OR) with 95 % confidence interval (CI) for diagnosed depression for individuals with type 2 diabetes screened for diabetes retinopathy at the time of the index date[a] according to level of diabetes retinopathy (level 0 used as reference).

Level of DR	Individuals with diagnosed depression	Individuals without diagnosed depression	OR (95%CI)		
			Crude model	Model adjusted for sex and age	Multivariable model[b]
Level 0	12,594	196,178	1 (Reference)	1 (Reference)	1 (Reference)
Level 1–4	1776	30,345	0.91 (0.87;0.96)	0.88 (0.83;0.93)	0.77 (0.73;0.82)
Level 1	1091	18,614	0.91 (0.86;0.97)	0.90 (0.84;0.96)	0.80 (0.75;0.86)
Level 2	353	6424	0.86 (0.77;0.95)	0.83 (0.74;0.92)	0.74 (0.66;0.83)
Level 3	63	1060	0.93 (0.72;1.19)	0.81 (0.63;1.04)	0.68 (0.52;0.91)
Level 4	269	4247	0.99 (0.87;1.12)	0.90 (0.79;1.02)	0.73 (0.64;0.84)

DR: diabetic retinopathy.
[a] Index date defined as the date of the first registration in the Danish Registry of Diabetic Retinopathy.
[b] Multivariable logistic regression model adjusted for age, sex, glucose-, lipid- or blood pressure lowering medication, marital status, HbA1c, diabetic neuropathy and an adjusted Charlson comorbidity index (myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, rheumatologic disease ulcer disease, hemiplegia or paraplegia, any malignancy (including leukemia and lymphoma), mild or moderate-severe liver disease, moderate-severe renal disease, and acquired immunodeficiency syndrome).

STATA version 17 (StataCorp LLC, College Station, TX, USA).

2.6. Ethics committee approval

The present study was part of the Ocular And Systemic complications In diabetic retinopathy Study (OASIS), emerging from the Danish Excellence Centre in Ophthalmic Epidemiology (DECODE-EYE).[21] The study was performed according to the tenets of the Helsinki Declaration, and relevant 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 Denmark, informed consent and permissions from the Danish National Committee on Health Research Ethics are not required for register-based studies.

3. Results

We included 240,893 individuals defined with type 2 diabetes who had attended the Danish DR-screening program during the defined interval (Fig. 1). Median age was 66.0 (IQR 56.6–73.4) years, and 56.9 % were male. A total of 208,772 (86.7 %) had no DR, and the prevalence of DR was 8.2 % (n = 19,705), 2.8 % (n = 6777), 0.5 % (n = 1123), and 1.9 % (n = 4516) for DR levels 1–4 respectively (Table 1). Individuals with DR were more often males, had longer diabetes duration, a higher comorbidity severity score, more often users of insulin, and had a higher level of HbA1c (Table 1).

We identified 14,370 individuals who were registered with diagnosed depression before index date (Table 2). Individuals with a registration of diagnosed depression were more often women (56.2 % vs. 42.3 %, $p < 0.001$), younger of age (60.5 vs. 66.3 years, $p < 0.001$), more often never married or widowed/divorced (20.9 % vs. 14.3 %, $p < 0.001$ and 36.0 % vs. 27.5 %, $p < 0.001$, respectively) and had a higher Charlson comorbidity index score (CCI ≥ 3: 10.9 % vs. 7.2 %, $p < 0.001$). Likewise, individuals registered with diagnosed depression were more often prescribed insulin (25.8 % vs. 21.6 %, $p < 0.001$), but less often prescribed blood pressure lowering (71.6 % vs. 77.1 %, $p < 0.001$) and cholesterol lowering drugs (69.9 % vs. 70.8 %, $p = 0.021$). There were no differences between groups regarding diabetes duration, use of glucose lowering drugs, excl. Insulin or HbA1c levels. (Table 2).

In a logistic regression model, individuals with DR were less likely to have a history of diagnosed depression at index date compared to individuals without DR (multivariable adjusted OR, 0.77 [95 % CI 0.73–0.82]) (Table 3). This was not statistically significant when the first registration of diagnosed depression was restricted to be given within two years prior to the index date (OR 0.81 [95 % CI 0.58–1.13]) (Supplementary material Table S1).

After individuals with diagnosed depression at index date were excluded (n = 14,370), the cohort was followed for overall 1,159,755 person-years. A total of 3827 individuals were registered with a diagnosed depression during a mean follow-up of 5.12 years. Compared to individuals without DR, individuals with DR had a higher risk of diagnosed depression (age- and sex adjusted model HR 1.25 [95 % CI 1.16–1.36]), but this was no longer statistically significant in the multivariable adjusted model (multivariable adjusted HR 1.02 [95 % CI 0.93–1.12]). This pattern persisted when we investigated the association across level specific DR (Table 4) and in the sensitivity analysis in which we did not utilize DR as a time-varying exposure (Supplementary material Table S2). We performed a post hoc analysis to investigate the risk of diagnosed depression in individuals who had undergone diabetes related procedures (Vitrectomy due to diabetes complications, focal and panretinal photocoagulation or anti vascular Endothelial Growth

Table 4
Hazard ratio (HR) with 95 % confidence interval (CI) for incident diagnosed depression after the index date[a] for individuals with type 2 diabetes screened for diabetic retinopathy according to level of diabetic retinopathy (Level 0 used as reference).

Level of DR	Events of diagnosed depression	Years of risk	HR(95%CI)		
			Crude model	Model adjusted for sex and age	Multivariable model[b]
0	3068	960,314.6	1 (Reference)	1 (Reference)	1 (Reference)
1–4	759	199,441.1	1.23 (1.13;1.33)	1.25 (1.16;1.36)	1.02 (0.93;1.12)
1	441	118,539.7	1.19 (1.08;1.32)	1.21 (1.09;1.33)	1.02 (0.91;1.14)
2	178	43,959.6	1.32 (1.14;1.54)	1.36 (1.17;1.59)	1.09 (0.92;1.29)
3	21	7089.6	0.96 (0.62;1.47)	1.02 (0.66;1.56)	0.83 (0.53;1.31)
4	119	29,852.3	1.30 (1.08;1.56)	1.33 (1.10;1.60)	0.95 (0.78;1.16)

DR: diabetic retinopathy.
[a] Index date defined as the first date of the registration in the Danish Registry of Diabetic Retinopathy.
[b] Multivariable Cox regression model adjusted for age, sex, glucose-, lipid- or blood pressure lowering medication, marital status, HbA1c, diabetic neuropathy, and an adjusted Charlson comorbidity index (myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, rheumatologic disease ulcer disease, hemiplegia or paraplegia, any malignancy (including leukemia and lymphoma), mild or moderate-severe liver disease, moderate-severe renal disease, and acquired immunodeficiency syndrome).

Table 5
Hazard ratio (HR) with 95 % confidence interval (CI) for diabetic retinopathy developing in at least one eye according to occurrence of diagnosed depression at the time of the index date[a] in the Danish Registry of Diabetic Retinopathy.

	Diagnosed depression		No diagnosed depression		HR (95 % CI)		
	Events	Person-years	Events	Person-years	Crude model	Model adjusted for sex and age	Multivariable model[c]
Incident DR[b]	1185	44,778.3	21,463	800,942.5	0.99 (0.93;1.05)	0.95 (0.90;1.01)	0.89 (0.77;1.03)
	Diagnosed depression within two year of index date		No diagnosed depression within two year of index date				
Incident DR[b]	157	4941.3	22,491	840,779.5	1.19 (1.02;1.39)	1.14 (0.98;1.34)	0.98 (0.68;1.42)
	Diagnosed depression within one year of index date		No diagnosed depression within one year of index date				
Incident DR[b]	75	2296.5	22,573	843,424.3	1.22 (0.97;1.53)	1.17 (0.93;1.47)	0.81 (0.46;1.43)

DR: diabetic retinopathy.
[a] Index date defined as the first date of the first registration in the Danish Registry of Diabetic Retinopathy.
[b] Given as the number of individuals with a new registration of DR level 1–4 (according to the International Clinical Retinopathy Disease Severity Scale) in at least one eye after the index date.
[c] Multivariable Cox regression model adjusted for age, sex, glucose-, lipid- or blood pressure lowering medication, marital status, HbA1c, diabetic neuropathy, and an adjusted Charlson comorbidity index (myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, rheumatologic disease ulcer disease, hemiplegia or paraplegia, any malignancy (including leukemia and lymphoma), mild or moderate-severe liver disease, moderate-severe renal disease, and acquired immunodeficiency syndrome).

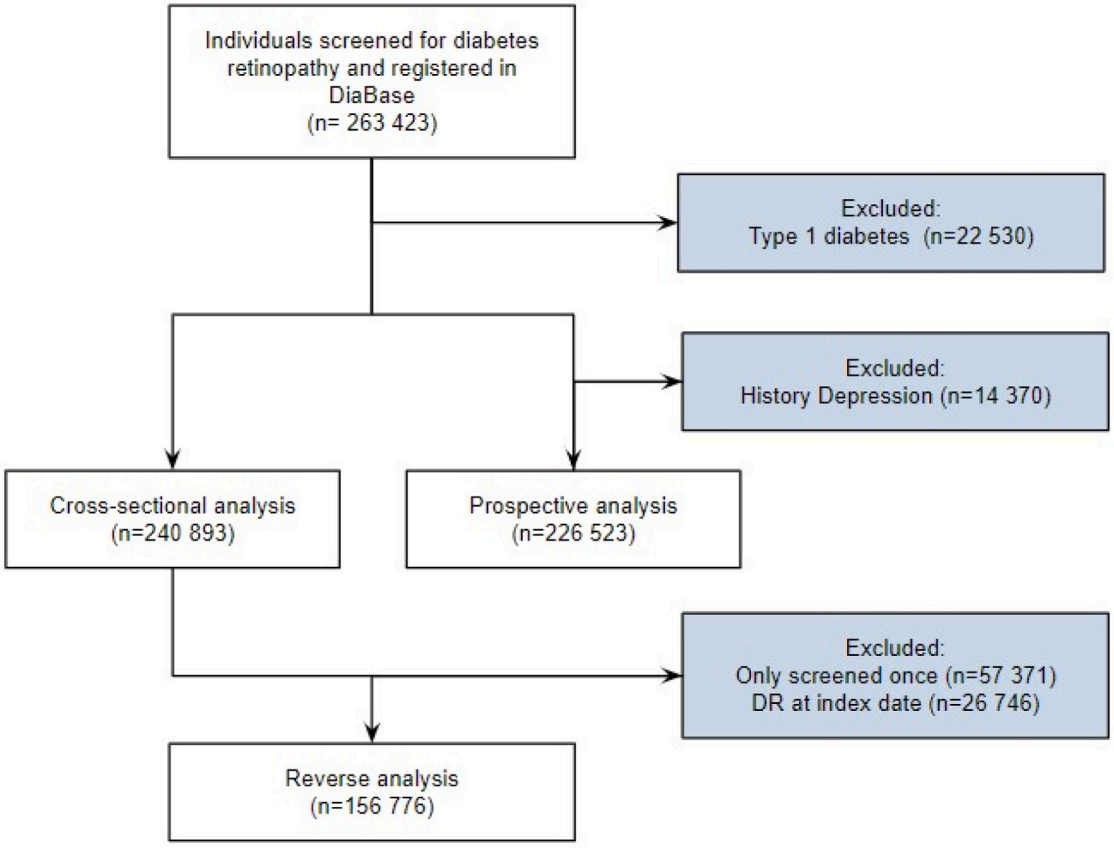

Fig. 1. Flowchart of inclusion.

Factor) and found no increased risk compared to individuals without DR or any procedures performed (Supplementary material Table S3).

To test if diagnosed depression could predict incident DR, individuals with DR at index were excluded. Thereafter, 8582 and 148,194 individuals with and without diagnosed depression were followed for 44,778 and 800,943 person years, respectively. In multivariable adjusted Cox regression analysis, a history of depression was not associated with incident DR (HR 0.89 [95 % CI 0.77–1.03]). In a sensitivity analysis where we restricted the registration of diagnosed depression to be given within one or two years before index date the association was no longer statistically significant (multivariable adjusted HR 0.81 [95 % CI 0.0.46–1.43] & multivariable adjusted HR 0.98 [95 % CI 0.68–1.42], respectively) (Table 5).

4. Discussion

In this nationwide cohort registry-based study of almost a quarter of a million individuals with type 2 diabetes, individuals with type 2 diabetes and DR were 23 % less likely to have been registered with diagnosed depression before index date. We did not find DR to be independently associated with an increased risk of diagnosed depression or that individuals with a history of diagnosed depression had a higher risk of incident DR during follow-up.

Interestingly, individuals with DR had a 23 % lower prevalence rate of a history of diagnosed depression but this association was no longer significant after we restricted the diagnoses of depression to be given within two years prior to the index date. We cannot rule out a potential pathophysiological association, but we speculate that the results may reflect our study population is based on a screening population. In a previous study of individuals attending the Danish screening program of DR, one time attendees had more often severe stages of DR, more comorbidity, lower income and shorter educational background.[22] Likewise mental illness including depression has been associated with non-attendance in DR screening programs.[23] Considering these two aspects, the lower rate of prevalent diagnosed depression in our study may be caused by study design meaning that individuals not attending the Danish screening program may be more prone to have both depression and DR.

In the last decades, much work has been done to uncover the association between diabetes complications and depression, but literature regarding DR and depression remains scare. Several possible pathophysiological mechanisms have been proposed between depression and DR including dysregulation of the hypothalamic-pituitary-adrenal axis and elevation of cortisol, which subsequently may lead to glycemic fluctuations and finally DR.[24,25] On the contrary, DR may cause depression because of visual impairment or fear of losing sight.[8] To our knowledge, only one longitudinal study has previously investigated the association between DR and the risk of incident depression in people with type 2 diabetes. In that German prospective study of 90,412 individuals with type 2 diabetes by Jacob et al., DR was found to be a risk factor of incident depression (HR 1.44 [95 % CI 1.21–1.70]) after adjustment for sex, private insurance, nephropathy, neuropathy, coronary heart disease, myocardial infarction, peripheral artery disease, hypertension, obesity and glucose lowering treatment.[9] Discrepancy in results between their and our findings may be caused by various reasons, including a difference in study populations, DR assessment and statistical methodology. Jacob et al. used ICD-10 code E11.3 (*Type 2 diabetes mellitus with ophthalmic complications*) for DR assessment, whereas we used nationwide screening results performed by ophthalmologists based on national guidelines. The ICD-10 code E11.3 also include diabetic cataract, which might decrease the accuracy of the DR assessment. The authors also stated that the prevalence of DR in the study did not accurately reflect the situation in Germany. Lastly Jacob et al. did not include age, civil status or HbA_{1c} in their multivariable adjusted model, which may also be important confounding covariates. In summary, comparing the results in the study by Jacob et al. and our study reveals differences in design and statistical approach, which we believe explain the differences in reported results.

We did not find a history of diagnosed depression to increase the risk of incident DR In a recent meta-analysis of ten cross-sectional and one prospective studies, Zou et al. reported a positive association between depression and DR (fixed-effects OR 1.50 [95 % CI 1.39–1.63]).[11] To our knowledge, only one prospective study have investigated the risk of incident DR in individuals with type 2 diabetes and depression, that found a slightly increased risk of DR in individuals with baseline depression (HR 1.03 95 % CI 1.01–1.04).[10] We would expect a history of diagnosed depression to increase the risk of incident DR, but this needs to be addressed further in larger prospective studies.

The strengths of our study include a large well-defined cohort of almost a quarter of a million individuals with type 2 diabetes and the use of national registries with valid, accurate and high completeness, which reduces the risk of misclassification. In addition we were able to use register data in combination with clinical and biochemical data. Another strength is our time-varying model where we took changes in life-events in to account e.g. marital status. Furthermore, we were able to investigate the bidirectional association, including DR level-specific risk assessment. Limitations to our study should also be acknowledged. The majority of mild to moderate depression is treated by general practitioners, hence these individuals are not necessarily included in this study, while treatment in the primary sector is not registered in the DNPR. Therefore, the depression cases in this study may be regarded as more severe cases. The registers do not hold information regarding visual acuity or race/ethnicity, which may be an important confounder. Lastly, our findings can only be generalized to individuals with type 2 diabetes that attend a DR screening program.

In this nationwide study of almost a quarter of a million individuals with type 2 diabetes those with DR were 23 % less likely to have a history of diagnosed depression, but DR did not independently predict incident diagnosed depression. A history of diagnosed depression was not associated with an increased risk of incident DR. Further studies are warranted in order to investigate whether these results can be replicated outside a screening population.

Funding

This work was supported by VELUX FONDEN (grant number 00028744) and Odense University Hospital PhD Foundation (grant number 4339).

Role of the funder

The funding organs had no role in the design of the study.

CRediT authorship contribution statement

All authors contributed to the study origin and design. Data collection and all analyzes were performed by Frederik Pedersen, Lonny Merete Stokholm, and Sören Möller. The first draft of the manuscript was authored by Anne Suhr Thykjær, and all authors commented, contributed and approved this and following drafts, including the final manuscript.

Declaration of competing interest

None reported.

Data availability

The datasets created and analyzed during the current study are available from the Danish Health Data Authority and Statistics Denmark, but restrictions apply to the availability of these data, which were used under license from OPEN and the Danish Health Data

Authority and are not publicly available.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2023.108589.

References

1 Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. *J Affect Disord*. 2012;142:S8–21.
2 Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care*. 2000;23:934–942.
3 Sivertsen H, Bjorklof GH, Engedal K, Selbaek G, Helvik AS. Depression and quality of life in older persons: a review. *Dement Geriatr Cogn Disord*. 2015;40:311–339.
4 van Dooren FE, Nefs G, Schram MT, Verhey FR, Denollet J, Pouwer F. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. *PloS One*. 2013;8, e57058.
5 Grauslund J, Green A, Sjolie AK. Prevalence and 25 year incidence of proliferative retinopathy among Danish type 1 diabetic patients. *Diabetologia*. 2009;52:1829–1835.
6 Grauslund J, Green A, Sjølie AK. Blindness in a 25-year follow-up of a population-based cohort of Danish type 1 diabetic patients. *Ophthalmology*. 2009;116:2170–2174.
7 Gonzalez JS, Peyrot M, McCarl LA, et al. Depression and diabetes treatment nonadherence: a meta-analysis. *Diabetes Care*. 2008;31:2398–2403.
8 Evans JR, Fletcher AE, Wormald RP. Depression and anxiety in visually impaired older people. *Ophthalmology*. 2007;114:283–288.
9 Jacob L, Kostev K. Prevalence of depression in type 2 diabetes patients in German primary care practices. *J Diabetes Complications*. 2016;30:432–437.
10 Sieu N, Katon W, Lin EH, Russo J, Ludman E, Ciechanowski P. Depression and incident diabetic retinopathy: a prospective cohort study. *Gen Hosp Psychiatry*. 2011;33:429–435.
11 Zou Y, You W, Wang J, et al. Depression and retinopathy in patients with type 2 diabetes mellitus: a meta-analysis. *Psychosom Med*. 2021;83:239–246.
12 Andersen N, Hjortdal J, Schielke KC, et al. The Danish registry of diabetic retinopathy. *Clin Epidemiol*. 2016;8:613–619.
13 Grauslund J, Andersen N, Andresen J, et al. Evidence-based Danish guidelines for screening of diabetic retinopathy. *Acta Ophthalmol*. 2018;96:763–769.
14 Wilkinson CP, Ferris 3rd FL, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*. 2003;110:1677–1682.
15 Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490.
16 Kildemoes HW, Sorensen HT, Hallas J. The Danish national prescription registry. *Scand J Public Health*. 2011;39:38–41.
17. Techniques for scatter and local photocoagulation treatment of diabetic retinopathy: Early Treatment Diabetic Retinopathy Study Report no. 3. The Early Treatment Diabetic Retinopathy Study Research Group. *Int Ophthalmol Clin*. 1987;27:254–264.
18. Laboratoriedatabasen. The Danish Health Data Authority. Available from: https://sundhedsdatastyrelsendk/da/registre-og-services/om-de-nationale-sundhedsregistre/doedsaarsager-og-biologisk-materiale/laboratoriedatabasen; 2022. Accessed November 30.
19 Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541–549.
20 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;173:676–682.
21 Grauslund J, Stokholm L, Ohm Kyvik K, Dornonville de la Cour M, Kessel L, Hass RK. 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;98:573–578.
22 Thykjaer AS, Andersen N, Bek T, et al. Attendance in a national screening program for diabetic retinopathy: a population-based study of 205,970 patients. *Acta Diabetol*. 2022;59:1493–1503.
23 Bradley ER, Delaffon V. Diabetic retinopathy screening in persons with mental illness: a literature review. *BMJ Open Ophthalmol*. 2020;5, e000437.
24 Golden SH. A review of the evidence for a neuroendocrine link between stress, depression and diabetes mellitus. *Curr Diabetes Rev*. 2007;3:252–259.
25 Musselman DL, Betan E, Larsen H, Phillips LS. Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. *Biol Psychiatry*. 2003;54:317–329.