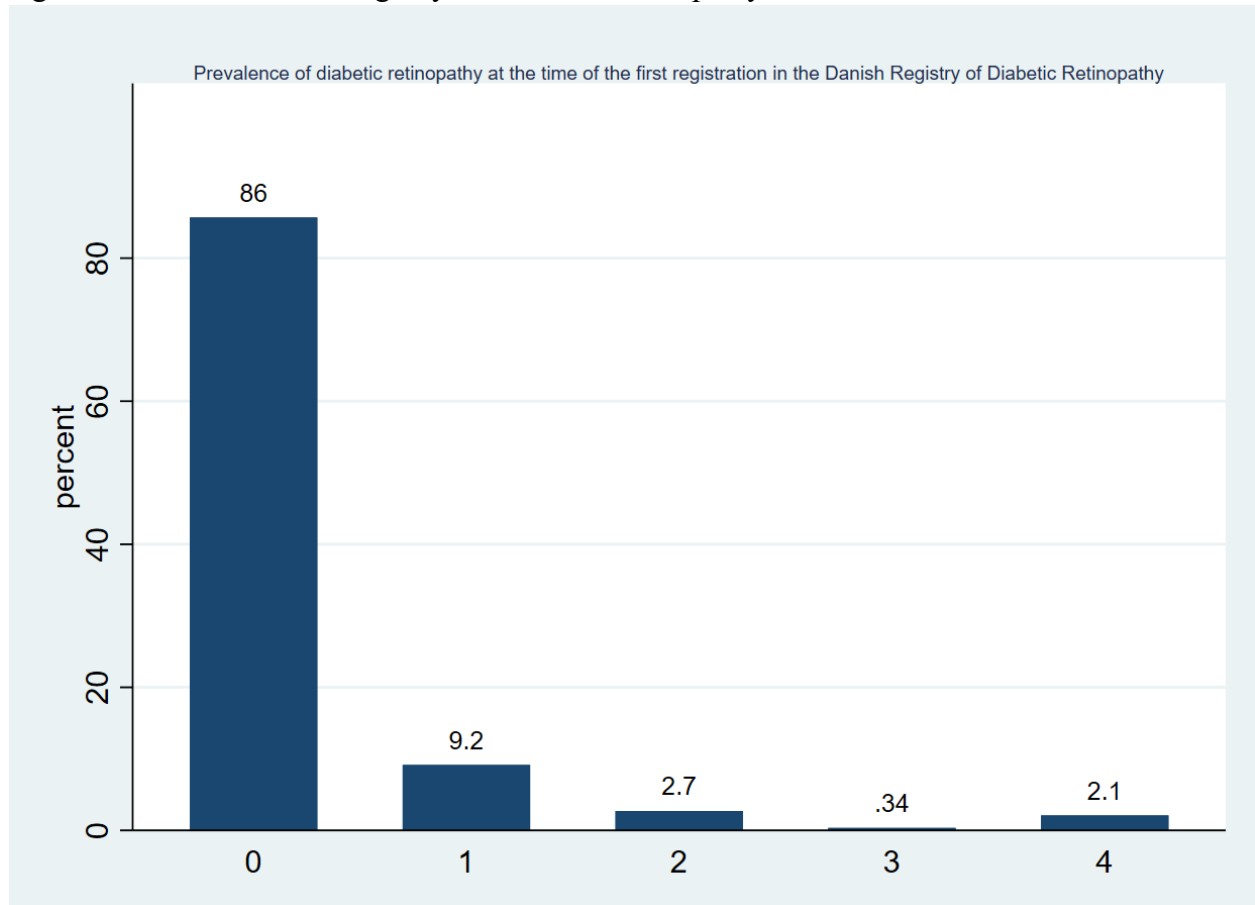


Supplementary Material

Diabetic Retinopathy Predicts Risk of Alzheimer's Disease: A Danish Registry-Based Nationwide Cohort Study

Supplementary Figure 1. Prevalence of diabetic retinopathy (Level 0-4) at the time of the first registration in the Danish Registry of Diabetic Retinopathy.



Supplementary Table 1. Type of diabetes determined according to International Classification of Diseases (ICD) version 10 codes for diabetes and Anatomical Therapeutic Chemical Classification (ATC) codes for treatment of diabetes given at the time of the first entry in the Danish Registry of Diabetic Retinopathy.

ICD version 10 code for diabetes		ATC code for diabetes treatment		Type of diabetes
DE10 ^a	DE11 ^b	A10A ^c	A10B ^d	
Yes	No	No	No	Unknown
Yes	Yes	No	No	Unknown
Yes	No	Yes	No	Type 1 diabetes
Yes	No	No	Yes	Unknown
Yes	No	Yes	Yes	Type 1 diabetes
Yes	Yes	No	Yes	Unknown
Yes	Yes	Yes	No	Unknown
Yes	Yes	Yes	Yes	Unknown
No	Yes	No	No	Type 2 diabetes
No	No	Yes	No	Unknown
No	No	No	Yes	Type 2 diabetes
No	Yes	Yes	No	Type 2 diabetes
No	Yes	No	Yes	Type 2 diabetes
No	No	Yes	Yes	Type 2 diabetes
No	Yes	Yes	Yes	Type 2 diabetes
No	No	No	No	Type 2 diabetes

*ICD codes: DE10^a, type 1 diabetes; DE11^b, type 2 diabetes. ATC codes for redeemed prescriptions: A10A^c, insulin; A10B^d, blood glucose lowering drugs excl. insulins.

Supplementary Table 2. Characteristics for persons screened for diabetic retinopathy (DR) at the time of the first registration in the Danish Registry of Diabetic Retinopathy according to the level of DR.

	Overall	Level of DR					p
		Level 0	Level 1	Level 2	Level 3	Level 4	
Number of persons, n	134,327	115,106	12,300	3,652	463	2,806	
Gender % male	(56.2)	(55.7)	(58.7)	(58.8)	(63.7)	(60.7)	<0.001
Age, y (IQR)	70.8 (66.0;76.5)	70.9 (66.1;76.5)	70.8 (66.0;76.9)	69.8 (65.1;75.6)	68.4 (64.2;73.3)	69.8 (65.2;75.4)	<0.001
Type of diabetes, n (%)							<0.001
Type 1 diabetes	3,464 (2.6)	1,746 (1.5)	986 (8.0)	246 (6.7)	28 (6.0)	458 (16.3)	
Type 2 diabetes	107,765 (80.2)	98,357 (85.4)	6,788 (55.2)	1,722 (47.2)	208 (44.9)	690 (24.6)	
Unknown	23,098 (17.2)	15,003 (13.0)	4,526 (36.8)	1,684 (46.1)	227 (49.0)	1,658 (59.1)	
Duration of diabetes, y (IQR)^a							<0.001
Type 1 diabetes	19.8 (13.3;21.5)	17.1 (7.3;21.0)	20.2 (19.3;21.9)	20.3 (19.2;22.2)	20.3 (19.1;21.8)	20.4 (19.6;22.2)	
Type 2 diabetes	6.2 (2.7;10.7)	5.8 (2.5;10.0)	11.6 (6.2;16.4)	12.3 (6.6;17.0)	13.6 (7.6;18.3)	15.7 (10.0;19.5)	
Unknown	15.1 (9.9;19.5)	12.7 (8.0;17.4)	18.7 (14.5;20.2)	18.7 (14.4;20.3)	18.6 (14.9;20.3)	19.9 (18.3;21.1)	
Marital status, n (%)							0.036
Never married	9,937 (7.4)	8,225 (7.1)	1,035 (8.4)	339 (9.3)	44 (9.5)	294 (10.5)	
Married	79,872 (59.5)	68,888 (59.8)	7,068 (57.5)	2,064 (56.5)	249 (53.8)	1,603 (57.1)	

Widowed or divorced	44,518 (33.1)	37,993 (33.0)	4,197 (34.1)	1,249 (34.2)	170 (36.7)	909 (32.4)	
Charlson Comorbidity Index score, n (%)							<0.001
0 (low)	92,329 (68.7)	82,479 (71.7)	6,812 (55.4)	1,823 (49.9)	203 (43.8)	1,012 (36.1)	
1 (moderate low)	17,964 (13.4)	13,000 (11.3)	2,773 (22.5)	982 (26.9)	141 (30.5)	1,068 (38.1)	
2 (Moderate high)	14,815 (11.0)	12,530 (10.9)	1,443 (11.7)	429 (11.7)	63 (13.6)	350 (12.5)	
≥3 (high)	9,219 (6.9)	7,097 (6.2)	1,272 (10.3)	418 (11.4)	56 (12.1)	376 (13.4)	
Use of medication, n (%)							
Insulin	36,866 (27.4)	24,068 (20.9)	7,444 (60.5)	2,620 (71.7)	358 (77.3)	2,376 (84.7)	<0.001
Glucose lowering treatment, excl. insulins	106,764 (79.5)	93,964 (81.6)	8,666 (70.5)	2,541 (69.6)	311 (67.2)	1,282 (45.7)	<0.001
Antihypertensive drugs	114,038 (84.9)	96,758 (84.1)	11,004 (89.5)	3,284 (89.9)	409 (88.3)	2,583 (92.1)	<0.001
Lipid lowering drugs	107,687 (80.2)	91,981 (79.9)	10,089 (82.0)	2,923 (80.0)	364 (78.6)	2,330 (83.0)	<0.001
Alzheimer's disease, n (%)	1,007 (0.7)	845 (0.7)	107 (0.9)	33 (0.9)		22 ^b (0.67)	<0.001
Depression, n (%)	5,891 (4.4)	5,079 (4.4)	507 (4.1)	159 (4.4)	15 (3.2)	131 (4.7)	0.030

Results are given as numbers, medians with interquartile ranges (IQR) or percentages. ^aDuration of diabetes was only calculated in persons with at least one International Classification of Diseases version 10 code for diabetes or one Anatomical Therapeutic Chemical Classification codes for treatment of diabetes. ^bDR level 3 and DR level 4 were pooled because of small samples.

Supplementary Table 3. Odds ratio (OR) with 95% confidence interval (CI) for Alzheimer’s disease (AD) for persons screened for diabetic retinopathy (DR) at the time of the index date^a according to the level of DR (level 0 used as reference).

Level of DR	Persons with AD	Persons without AD	Crude model	Model adjusted for sex and age	Multivariable model^b
			OR (95% CI)	OR (95% CI)	OR (95% CI)
Level 1-4	162	19,059	1.15 (0.97-1.36)	1.15 (0.97-1.37)	1.16 (0.98-1.38)
Level 0	845	114,261	1 (reference)	1 (reference)	1 (reference)

^aIndex date defined as the date of the first registration in the Danish Registry of Diabetic Retinopathy for persons with diabetes.

^bMultivariable logistic regression model adjusted for sex, age, depression, marital status, use of antihypertensive drugs, lipid lowering drugs and Charlson comorbidity index: myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, connective tissue disease and rheumatologic disease, ulcer disease, mild or moderate-severe liver disease, renal disease, hemiplegia or paraplegia, any malignancies (including leukemia and lymphoma), and acquired immunodeficiency syndrome.