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Severe Diabetic Retinal Disease and Dementia Risk in Type 2 Diabetes

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Abstract

Background—Persons with type 2 diabetes are at an increased risk of dementia compared to those without, but the etiology of this increased risk is unclear.

Objective—Cerebral microvascular disease may mediate the link between diabetes and dementia. Given the anatomical and physiological similarities between cerebral and retinal microvessels, we examined the longitudinal association between diabetic retinal disease and dementia in patients with type 2 diabetes.

Methods—Longitudinal cohort study of 29,961 patients with type 2 diabetes aged 60 years. Electronic medical records were used to collect diagnoses and treatment of severe diabetic retinal disease (i.e. diabetic proliferative retinopathy and macular edema) between 1996–1998 and dementia diagnoses for the next ten years (1998–2008). The association between diabetic retinal disease and dementia was evaluated by Cox proportional hazard models adjusted for sociodemographics, and also for diabetes-specific (e.g. diabetes duration, pharmacotherapy, HbA1c, hypoglycaemia, hyperglycemia) and vascular factors (e.g. vascular disease, smoking, BMI).

Results—2008 (6.8%) patients had severe diabetic retinal disease at baseline and 5173 (17.3%) participants were diagnosed with dementia during follow-up. Those with diabetic retinal disease had a 42% increased risk of incident dementia (demographics adjusted Hazards Ratio (HR)=1.42, 95% Confidence Interval (CI) 1.27, 1.58) further adjustment for diabetes-specific (HR1.29; 95%CI 1.14,1.45) and vascular-related disease conditions (HR 1.35; 95%CI 1.21,1.52) attenuated the relation slightly.

Conclusion—Diabetic patients with severe diabetic retinal disease have an increased risk of dementia. This may reflect a causal link between microvascular disease and dementia.

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Keywords

diabetes; retinal disease; retinopathy; macular edema; dementia; microvascular disease

Introduction

Elderly people with type 2 diabetes (T2DM) have approximately a two-fold greater risk of dementia, both Alzheimer's Disease (AD) and Vascular dementia, compared to elderly people without diabetes [1]. At present the aetiology behind this increased risk is unknown. In autopsy studies, T2DM is associated with more pronounced vascular pathology in the brain, but not with increased AD-type pathology [2–4]. The former is not surprising, considering that T2DM is associated with vascular complications, including both micro- and macrovascular disease. The brain of T2DM patients is thus likely a site of more pronounced microvascular pathology, whether or not in association with large-vessel brain pathology. Direct *in vivo* evaluation of the cerebral microvasculature is difficult. Abnormalities in the retinal microvasculature may represent a proxy for cerebral microvascular disease, as the microvessels in the brain share many morphological and physiological similarities with those in the retina. In contrast to the cerebral microvessels, the retinal bloodvessels can be directly visualized in a noninvasive manner. Microvascular changes in the retina can therefore offer a window into the microvasculature of the brain [5,6].

In the general population, retinal microvascular changes have been correlated with dementia and cognitive impairment [7]. It is of particular relevance to study this association in patients with existing T2DM, as diabetes can lead to pronounced microvascular changes. Previous studies observed associations between diabetic retinal disease and lower cognitive performance [8–10], but results are inconsistent [11,12]. However, these studies were mostly cross-sectional and the possible prospective link between diabetic retinal disease and the incidence of dementia has not been studied previously.

Identifying mutual disease processes of T2DM and dementia could further elucidate the aetiology of their association. If microvascular changes indeed play a role in the aetiology of dementia in patients with T2DM, it is expected that the presence of severe diabetic retinal disease (such as diabetic proliferative retinopathy and diabetic macular edema) is associated with dementia. The objective of this study was to determine whether severe diabetic retinal disease is associated with an increased incidence of dementia identified during 10 years of follow-up in a large well-characterized cohort of older patients with T2DM.

Research Design and Methods

Population

We evaluated 29,961 patients aged ≥60 years) with T2DM who were members of the Kaiser Permanente Northern California (KPNC) Diabetes Registry ("Registry"). This well characterized cohort of patients with diabetes has been the basis of several epidemiologic and health services studies [13–16] since 1994, as part of the Diabetes and Aging study. KPNC is a large, integrated health care delivery system providing comprehensive medical services to ~3.3 million members, representing ~30% of the surrounding population. Its

membership closely approximates the general population by race/ethnicity and socioeconomic status with exception for slight underrepresentation of individuals in the extreme tails of income distribution.[17]

Analytic Cohort

The Registry identifies individuals with diabetes from five sources of electronic medical records, with an estimated sensitivity of 99% based on chart review validation. The five 5 sources are: outpatient encounter files (diagnosis of diabetes); pharmacy prescriptions for diabetes medications; glycosylated hemoglobin (HbA1c) values greater than 7% in laboratory files; primary hospital discharge diagnoses of diabetes; and emergency room diagnoses records of diabetes as the reason for visit [13]. Between 1994–1997, all members of the Registry were mailed a survey to collect sociodemographic and health behaviours information (response rate 83%). Previously, we found no indication of bias from differences in characteristics or epidemiologic associations by survey respondent status [18,19]. Patients participating in the survey with T2DM were eligible for our analytic cohort (N=62,616). Further inclusion criteria were: i) alive at baseline (January 1, 1998); ii) no dementia diagnosis at baseline; iii) no gap of 3 months in health plan membership during the two years prior to baseline; and iv) age 60 years at baseline. The final cohort consisted of 29,961 patients.

Data were collected using data from the survey and the combined electronic medical record data which incorporates laboratory test results, pharmacy, inpatient and outpatient diagnoses. The KP pharmacy data is computer-stored data on outpatient prescriptions filled in KP pharmacies. We defined a medication as dispensed if there was at least one fill for a prescription for a given medication, with at least a 30 days' supply, within the 6 months prior to baseline. Previous studies have validated the identification schemes of these covariates in this population [20]. From 1996 onwards all KPNC locations had electronic medical records. This enabled us to identify diabetic retinal disease based on the medical records two years prior to baseline (i.e. from January 1, 1996 till January 1, 1998). Sociodemographic factors, medical utilization, diabetes related factors and vascular factors were also collected during these two years. Dementia diagnoses were identified for 10 years from January 1, 1998 onwards.

Data Collection

Dementia Diagnoses—Diagnoses of dementia were identified from medical records between 1/1/1998–1/1/2008 with the use of *ICD-9-CM* diagnosis codes; senile dementia uncomplicated (290. 0), Alzheimer disease (331.0), vascular dementia (290.4x), and dementia not otherwise specified (290.1). Using diagnoses made in primary care (ICD 9 codes 290.0, 290.1x) and neurology or memory clinic visits (ICD 9 codes 331.0, 290.1x, 290.2x, 290.3, 290.4x). This strategy was found to have a sensitivity of 77% and specificity of 95% compared to a consensus diagnosis of dementia based on a neuropsychiatric battery, physical examination, structured interview with informants, and review of medical records [21].

Exposure variable—For the purpose of this study diabetic retinal disease was defined as proliferative diabetic retinopathy and/or diabetic macular edema identified between 1/1/1996–1/1/1998 using either records for inpatient treatment: (for proliferative diabetic retinopathy: panretinal photocoagulation to treat proliferative retinopathy (CTP4 code 67228), for diabetic macular edema: focal and grid photocoagulation to treat macular edema (CTP4 codes 67208 67210); or outpatient diagnoses made in ophthalmology: (ICD 9 codes 250.5 + 362.02 for proliferative diabetic retinopathy; ICD 9 codes 250.5 + 362.53 or 250.5 + 362.83 for diabetic macular edema). To restrict false positive diagnosis of diabetic retinal disease, only the severe sight threatening diabetic retinal disease forms (proliferative diabetic retinopathy and diabetic macular edema) were included.

Sociodemographics—Age, gender, education, and race/ethnicity were based on self-reported data from the survey. Education level indicates the highest finished level: 1) Grade school, 2) High school 3) High school graduate, 4) Trade/business school, 5) College graduate, 6) Graduate School. Race/ethnicity included 6 categories in which the patients could self-identify, namely white, African American, Asian, Hispanic, Native American, or other.

Medical utilization—Medical utilization rate was determined by collecting the number of medical visits per year during the follow-up period, divided by year to determine an aggregated rate.

Diabetes specific factors—Duration of diabetes was based on self-reported data from the survey. Diabetes pharmacotherapy was evaluated using the Kaiser Permanente (KP) pharmacy databases. Diabetes pharmacotherapy was classified as: insulin only, oral agent only (i.e. insulin secretagogues such as sulfonylureas or insulin sensitizers such as metformin and thiazolidinediones), insulin and oral agent combined, or no pharmacotherapy treatment (i.e. neither insulin nor oral agent prescriptions). Diagnoses of severe episodes of hyperglycemia resulting in an emergency room visit or hospitalization (ICD 9codes 250.1,250.2, 249.2), severe hypoglycemia resulting in an emergency room visit or hospitalization (251.0–2). We used the most recent HbA1c measurements reported in KP laboratory databases between 1/1/1996 and 1/1/1998. For additional statistical analysis, we created a composite measure of diabetes severity. The diabetes composite was defined by summing up the values of five criteria: 1) Diabetes duration (0 = <10 years, 1 = 10–15 years, 2 = >15 years), 2) HbA1c (0 = >5 and <12, 1 = 12, 2 = 5), 3) Insulin (1=Diabetes pharmacotherapy is insulin, 0 otherwise), 4) Hypoglycemia (0 = No, 1 = Yes), 5) Hyperglycemia (0 = No, 1 = Yes). The diabetes composite measure ranged from 0–7. The cut-off values for HbA1c and diabetes duration are based on previous work with this data [16].

Vascular factors—Smoking status (current, former, never) and body mass index (calculated as weight in kilograms divided by height in meters squared) were based on self-reported data from the survey. Hypertension and hyperlipidemia were defined using a combination of ICD9 codes and medication indicative for that condition [22] in the period 1-1-1996–1-1-1998. Hypertension was defined as either ICD 9 codes 401–405 or 1

dispensing of any antihypertensive medication (ACE inhibitor, alpha-blocker, beta-blocker, calcium channel blocker, centrally acting antihypertensive, diuretics, vasodilator) for at least a 30 days' supply. Hyperlipidemia was defined as either ICD 9 code 272 or 1 dispensing of any antilipemic medication (cholestyramine resin, colestipol hydrochloride, gemfibrozil, lovastatin, niacin, simvastatin) for at least a 30 days' supply. Diagnoses of myocardial infarction (MI) (ICD 9 codes 410, 412), cerebrovascular disease (CVD) (ICD 9 codes 431, 433, 434, 436, 442.81, 442.82, 433.x), peripheral arterial disease (PAD) (ICD 9 codes 440, 441, 442.0, 442.3, 443.81, 443.9) and congestive heart failure (CHF) (ICD 9 codes 401.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.93, 428.0, 428.1, 428.9, 4251) were collected from inpatient and outpatient databases (1/1/1996–1/1/1998). For statistical analysis, we created a composite measure of vascular disease. The vascular composite score was measured as a sum of six factors (all with values of 0 = No, 1 = Yes): cerebrovascular disease, hypertension, hyperlipidemia, peripheral artery disease, myocardial infarction, and congestive heart failure. The vascular composite measure ranged from 0–6.

Ethics

The study was approved by the institutional review board of Kaiser Permanente of Northern California and a waiver of informed consent was obtained due to the nature of the study.

Statistics

Patient characteristics by diabetic retinal disease status were compared using chi square analyses and t-tests. Incidence density rates of dementia were calculated for diabetic retinal disease, overall, and for each subcategory. Cox proportional hazard models were used for point and interval estimates of hazard ratios for time to dementia associated with diabetic retinal disease, with adjustment for covariates. Since dementia risk is more a function of age than time since baseline; age, rather than year, was used as the time scale in the Cox models [23]. Follow-up time commenced with patient age at start of dementia ascertainment on January 1, 1998, and stopped at the earliest of the following events: 1) age at incident dementia diagnosis, 2) age at termination of health plan membership (defined as a continuous membership gap of 3 months or greater), 3) age at death, or iv) age at end of the study period on January 1, 2008.

With the use of age as a time scale in fitting the Cox models, the model without covariates is already age adjusted (model 1). First we evaluated the link between diabetic retinal disease and dementia, taking into account potential confounding effects of demographic factors. We used cox models adjusted for age (as the time scale), gender, race/ethnicity and education (model 2). Next, medical utilization was added to model 2. If medical utilization attenuated the association it would be added to all the following models. The other individual covariates were divided in two groups; diabetes-specific and vascular factors. Many of these variables are interrelated, within the subgroups and between the two groups of covariates. First the individual covariates were added one by one to evaluate their potential individual role in contributing to any potential attenuation of the magnitude of the effect of diabetic retinal disease on dementia risk. A priori, these models were adjusted for sociodemographics. Next, two models were analysed for sociodemographics and either all five diabetes-specific or all eight vascular factors. Adjustments for all 17 covariates (i.a. all

diabetes-specific and all vascular factors) in one model would overfit our data. In order to be able to simultaneously adjust for a large number of variables in one model while keeping it parsimonious, we created composite measures of both diabetes severity and vascular disease. In the models with the composite scores, we included a priori the medical utilization rate, in order to account for the potential influence of frequency of health care visits during the follow-up.

Five and seven year lagged models were analyzed to force a greater temporal sequence between the occurrence of diabetic retinal disease and risk of dementia, such that only incident dementia cases occurring either from 1/1/2003 to 1/1/2008 (5-year) or from 1/1/2005 to 1/1/2008 (7-year) were considered. Finally, analyses of separate subtypes of diabetic retinal disease were evaluated for possible qualitatively different associations between dementia and proliferative diabetic retinopathy versus diabetic macular edema. We used a change in estimate approach to select covariates for these models. Individual covariates were selected if the variable changed the hazard ratio for dementia associated with diabetic retinal disease by more than 5%. For these models medical utilization rate was included a priori, in order to account for the potential influence of frequency of health care visits during the follow-up.

All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC), associations were considered significant at the 0.05 level.). In all models, assumptions of proportional hazards were met.

Results

The mean age of the cohort was 70.6 years (SD 6.8) at baseline, 46% female, and 37% non-caucasian (Table 1). Almost 7% of the patients had a diagnosis of diabetic retinal disease at baseline. Those with diabetic retinal disease were more likely to be female, non-Caucasian, taking insulin, were slightly younger and had a longer duration of diabetes and a higher average HbA1c. Those with diabetic retinal disease also had a higher prevalence of hyperglycaemic events, hypoglycaemic events, hypertension, hyperlipidemia, peripheral arterial disease, myocardial infarction and congestive heart failure.

A total of 5173 patients (17.3%) were diagnosed with dementia during a mean follow-up of 6.6 years, at an average age of 77.2 (SD 6.5). The incidence density rates for dementia were elevated among those with diabetic retinal disease (328.7 cases per 10,000 person years) compared to those without diabetic retinal disease (256.5 cases per 10,000 person years; Table 2).

In Cox proportional hazard models adjusted for sociodemographic variables (model 2), patients with diabetic retinal disease had a 42% increased risk of dementia compared to those without (Table 3). This association was not attenuated by medical utilization, on the contrary the magnitude of the effect of diabetic retinal disease on dementia risk increased to 47%. Therefore, medical utilization was not included in the models that were adjusted for individual variables. Further adjustment of model 2 with individual variables of diabetes-specific or vascular factors modestly attenuated the effect, although it remained significant

(Table 3). The largest attenuation was seen for diabetes pharmacotherapy (HR=1.32; 95% CI 1.18, 1.48). The results of the models that were simultaneously adjusted for all diabetes-specific variables or all the vascular factors variables (Table 3) are comparable with the models that were adjusted by the diabetes composite (HR=1.29, 95% CI 1.15, 1.45) or vascular composite (HR=1.39, 95% CI 1.24, 1.55). In the fully-adjusted model (sociodemographics, medical utilization, diabetes composite, BMI, smoking and vascular composite) patients with diabetic retinal disease had a 32% increased risk of dementia (Table 3).

The lagged cox proportional hazard models (i.e. only considering incident dementia cases that occurred between 1/1/2003 and 1/1/2008 (5-year) or 1/1/2005 to 1/1/2008 (7-year)) showed an attenuation of the association between diabetic retinal disease and dementia with a greater temporal sequence between the occurrence of diabetic retinal disease and incidence of dementia. In the five year lagged model diabetic retinal disease was associated with a 34% (HR=1.34, 95% CI 0.90 1.43) greater risk of dementia versus 18% (HR=1.18, 95% CI 0.01 1.39) in the seven year lagged model (both adjusted for age, gender, race, education, medical utilization and diabetes pharmacotherapy).

There were no qualitative differences between the two subtypes of diabetic retinal disease (proliferative diabetic retinopathy, or diabetic macular edema or both) and dementia risk (Table 4). Both types were associated with a 40% greater risk of dementia independent of one another.

Discussion

In our large population of elderly patients with type 2 diabetes, the presence of diabetic retinal disease is associated with an increased risk of dementia over a 10 year period. This association was attenuated by adjustments for diabetes-specific and by vascular factors. Our results suggest an association between diabetic retinal disease and dementia that was incompletely explained by diabetes-specific and vascular factors. This adds to the evidence that microvascular disease contributes to dementia in the context of T2DM.

Previous studies in patients with T2DM, focused on the association between diabetic retinal disease and cognitive impairment, rather than a clinical diagnosis of dementia. In cross-sectional studies diabetic retinal disease has been associated with a lower mini mental state examination score [10] and lower global cognitive ability (based on a standardized neuropsychological examination) [8,24]. A longitudinal study (n=180), reported that the presence of diabetic retinopathy assessed prior to coronary surgery was associated with an increased risk of cognitive decline after 6 months following surgery [9]. Other studies reported no association between diabetic retinopathy and cognition [11,12] nor with cognitive decline after 4 years [11]. Possible explanations for the negative findings of some of these studies include limited sample sizes (consequently including few retinopathy cases e.g. [11], different levels of severity of diabetic retinopathy (i.e. also including non-proliferative diabetic retinopathy a less severe form of diabetic retinal disease) [11] and exclusion of patients with dementia and stroke which could lead to an underestimate of the level of cognitive impairment [12]. Of note the relation between diabetic retinopathy and

cognition has also been studied in patients with type 1 diabetes. These studies found an association between diabetic retinopathy and reduced cognitive functioning [25,26] and abnormalities on brain MRI [27,28]. While these findings suggest a potential pathway between retinopathy and cerebral complications, patients with type 1 diabetes have a different aetiology, and are much younger than patients with T2DM. Furthermore, the prevalence of proliferative diabetic retinopathy and diabetic macular edema is substantially higher in type 1 compared with type 2 diabetes (32% vs 3%, 14% vs 6% respectively) [29].

In the general population, retinal microvascular changes have been linked to dementia and cognitive impairment as outcome measures [review: [7]]. Two studies in the general population, a cross-sectional (n=1767 [30]) and a longitudinal (n= 6078 [31]) design, stratified the association between retinopathy and dementia by diabetes status. The cross-sectional study found an association in the whole cohort, but not in the diabetic subgroup (n=289). The longitudinal study reported an association between retinopathy with prevalent dementia at baseline in the diabetic subgroup (n≈600), but found no association between retinopathy and 10 year dementia incidence. It should be noted, however, that the power of the previous studies was limited due to modest sample sizes. Furthermore, these studies examined any form of retinopathy while we only used the severe forms (proliferative diabetic retinopathy and diabetic macular edema). And the type of diabetes is not specified. In the general population, reported associations between retinal microvascular changes and dementia are strongest for more severe retinal microvascular abnormalities [7]. This has also been seen in T2DM; increasing severity of diabetic retinopathy was associated with poorer general cognitive ability [8]. The lagged cox proportional hazard models in the present study showed that the association between the diagnosis of diabetic retinal disease and the diagnosis of dementia is stronger when they are closer in time, but is still present with a seven year lag. This suggest that microvascular damage in the retina and brain are probably partly occurring at a similar time. Furthermore, there might be a delay before the microvascular damage in the brain has reached a level that causes clinical significant symptoms, i.e. dementia. This is in line with previous theories that brain changes and their accompanying biomarkers occur long before clinical significant cognitive impairment is present [32].

The pathophysiology of T2DM is complex, involving an interplay between endocrinological, metabolic and vascular abnormalities. Several of these abnormalities have been implicated in the pathophysiology of both dementia and diabetic retinal disease, however the exact mechanisms remain unknown. Chronic hyperglycemia, as well as hyperlipidemia and hypertension contribute to the pathogenesis of vascular disruptions of diabetic retinopathy and diabetic macular edema [33]. These factors are also involved in the possible mediating mechanisms for vascular changes linking T2DM to dementia [34]. Interestingly, the association between diabetic retinal disease and dementia was somewhat attenuated but remained statistically significant after adjustments for diabetes-specific and vascular factors. Especially, the combination of all diabetes-specific variables moderately attenuated the association, while individual factors barely attenuated the association. This suggests that the association between diabetic retinal disease and dementia might indeed be partially mediated by diabetes severity and to a lesser extent by concomitant vascular factors. The fact that the association between diabetic retinal disease and dementia remained

statistically significant after adjustments, might be explained by individual vulnerability to microvascular complications leading to both retinal and cerebral microvascular pathology. Overall, the presence of pronounced microvascular damage seems to contribute to dementia in the context of T2DM partially independent of suggested mutual mediating mechanisms. A better understanding of possible pathophysiological mechanism can be unravelled by investigating the different microvascular changes that occur in diabetic retinal disease. Diabetic proliferative retinopathy is characterized by the growth of abnormal retinal vessels and diabetic macular edema occurs after breakdown of the blood-retinal barrier. Interestingly, we found no qualitative differences between proliferative diabetic retinopathy and diabetic macular edema in the association with dementia. Further research is needed to unravel the pathophysiological mechanism underlying the association between diabetic retinal disease and dementia.

There are several strengths of the present study including a large well characterized cohort of patients with T2DM with detailed information on a wide breadth of comorbidities, including prior glycemic dysregulation, HbA1c levels, diabetes-pharmacotherapy and vascular disease. The longitudinal design allowed observation for incident dementia over a prolonged period. Finally, the study is embedded within a population consisting solely of those with type 2 diabetes, allowing the statistical power to examine the role of a diabetic complication (e.g. diabetic retinal disease) on dementia incidence while simultaneously taking into account the influence of type 2 diabetes itself on dementia.

A potential weakness of our study is the use of medical record diagnoses from an integrated health care delivery system, rather than the results of standardized cognitive or retinal assessments administered periodically to all cohort members. This may have resulted in under-recognition of some cases. Another potential concern is that due to the observational nature of our cohort study, we cannot be certain of the temporality of our findings. To address this, individuals with a diagnosis of dementia before 1998 were excluded; and we also conducted lagged analyses to increase the temporal separation of diabetic retinal disease from later occurrences of dementia.

In conclusion, the present study shows that among patients with T2DM, the presence of severe diabetic retinal disease is associated with dementia incidence during the following 10 years. Our study complements prior studies in several unique ways: our outcome is dementia, rather than cognitive function; we have 10 year follow-up of a large T2DM cohort and we extend the investigation by separately analysing diabetic macular edema. Our results suggest that microvascular disease contributes to the development of dementia in the context of T2DM. Further research is needed to unravel the underlying aetiology of microvascular changes and its role in the development of dementia.

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Table 1

Population Characteristics at Baseline

	All (N=29961)	Diabetic Retinal Disease (N=2008)	Diabetic Retinal Disease absent (N=27953)	P value
Age in 1998, y	70.6 (6.8)	70.0 (6.4)	70.6 (6.8)	<.001
Female	13787(46.0%)	1028 (51.2 %)	12759 (45.6%)	<.001
Race				<.001
White	18903(63.1%)	1137 (56.6%)	17766 (63.6%)	
African Amer.	3400 (11.4%)	279 (13.9%)	3121 (11.2%)	
Hispanic	3291 (11.0%)	272 (13.6%)	3019 (10.8%)	
Asian	3246 (10.8%)	238 (11.9%)	3008 (10.8%)	
Other	820 (2.8%)	59 (3.0%)	761 (2.8%)	
Education level, range 1–6	4 (3–5)	4 (3–5)	4 (3–5)	0.42
Medical utilization	7059 (23.6%)	622 (31.0%)	6437 (23.0%)	<.001
Diabetes Duration, y	11.6 (9.5)	16.1 (9.8)	11.3 (9.4)	<.001
HbA1c, %	7.8 (1.8)	8.0 (1.9)	7.8 (1.8)	<.001
Diabetespharmacotherapy				<.001
None	5934 (19.8%)	197 (9.8%)	5737 (20.5%)	
Insulin Only	5905 (19.7%)	860 (42.8%)	5045 (18.1%)	
Oral Only	16247(54.2%)	746 (37.2%)	15501 (55.5%)	
Insulin +Oral	1875 (6.3%)	205 (10.2%)	1670 (6.0%)	
Hyperglycemic events	99 (0.3%)	14 (0.7%)	85 (0.3%)	<.005
Hypoglycemic events	962 (3.2%)	156 (7.8%)	806 (2.9%)	<.001
Cerebrovascular disease	2149 (7.2%)	198 (9.9%)	1951 (7.0%)	<.001
Hypertension	17577(58.7%)	1316(65.5%)	16261(58.2%)	<.001
Hyperlipidemia	6348 (21.2%)	463 (23.1%)	5885 (21.1%)	0.03
BMI, kg/m2	29.0 (5.5)	28.8 (5.3)	29(5.5)	0.07
Smoking				<.001
Current	2275 (7.6%)	84 (1.2%)	2191 (7.8%)	
Former	12572(42.0%)	763 (38.0%)	11809 (42.3%)	
Never	12669(42.3%)	990 (49.3%)	11679 (41.8%)	
Peripheral arterial disease	1842 (6.2%)	208 (10.4%)	1634 (5.9%)	<.001
Myocardial infarction	4181 (14.0%)	332 (16.5%)	3849 (13.8%)	<.001
Congestive heart failure	3593 (12.0%)	382 (19.0%)	3211 (11.5%)	<.001

Data are presented as number (column %) or mean (SD) and for education level median (interquartile range). P values were calculated using chi-square or student t-test, y=years. Education level: 1) Grade school, 2) High school 3)High school graduate, 4) Trade/business school, 5) College graduate, 6) Graduate School. Abbreviations: HbA1c, glycosylated hemoglobin; BMI, body mass index.

Table 2

Incidence Rates of Dementia by Diabetic Retinal Disease Status

	No. of Dementia cases	Total Person Years	Incidence Rate per 10,000 Person Years (95%CI)
No diabetic retinal disease N=27953	4787	186622.5	256.5 (249.2, 263.7)
Diabetic retinal disease N=2008	386	11743.1	328.7 (295.9, 361.4)
Proliferative retinopathy only N= 502	91	2837.4	320.7 (254.8,386.6)
Diabetic macular edema only N=1014	220	6025.2	365.1 (316.9, 413.4)

For the calculation of the incidence density rate of the groups with only DPR or only DME, patient with respectively DME and DPR were excluded.

Table 3

Diabetic Retinal Disease and Risk of Dementia from Age as Time Scale Cox Proportional Hazard Models

	Hazard ratio (95% CI)
Sociodemographics	
Model 1: age (as time scale)	1.41 (1.27 1.57)
Model 2: age (as time scale), gender, race and education.	1.42 (1.27 1.58)
Medical utilization	
Model 3: model 2 & medical utilization.	1.47 (1.32 1.64)
Diabetes associated factors	
Model 2 & diabetes duration	1.36 (1.22 1.52)
Model 2 & HbA1c	1.39 (1.24 1.56)
Model 2 & diabetes pharmacotherapy	1.32 (1.18 1.48)
Model 2 & hyperglycemia	1.42 (1.27 1.58)
Model 2 & hypoglycaemia	1.38 (1.24 1.54)
Model 2 & all five diabetes associated factors above	1.29 (1.14 1.45)
Vascular factors	
Model 2 & cerebrovascular disease	1.38 (1.24 1.54)
Model 2 & hypertension	1.42 (1.27 1.58)
Model 2 & hyperlipidemia	1.42 (1.27 1.58)
Model 2 & BMI	1.41 (1.26 1.58)
Model 2 & smoking status	1.42 (1.27 1.59)
Model 2 & peripheral arterial disease	1.39 (1.25 1.55)
Model 2 & myocardial infarction	1.41 (1.26 1.57)
Model 2 & congestive heart failure	1.38 (1.24 1.55)
Model 2 & all eight vascular factors above	1.35 (1.21 1.52)
Combined diabetes and vascular factors	
Model 3 & DM composite and Vascular composite	1.32 (1.17, 1.48)
Model 3 & DM composite, Vascular composite, BMI and smoking status	1.32 (1.17, 1.49)

Abbreviations: HbA1c, glycosylated hemoglobin; BMI, body mass index; DM, diabetes mellitus. Diabetes duration and HbA1c are analysed as continuous variables, but were categorized for the DM composite score, which includes diabetes duration (0 = <10 years, 1 = 10–15 years, 2 = >15 years), HbA1c (0 = >5 and <12, 1 = 12, 2 = 5), 3) use of insulin, hypoglycemic events and hyperglycemia events. Vascular composite includes presence of cerebrovascular disease, hypertension, hyperlipidemia, peripheral artery disease, myocardial infarction, and/or congestive heart failure.

Table 4

Type of Diabetic Retinal Disease and Risk of Dementia from Age as Time Scale Cox Proportional Hazard Models

	Hazard ratio (95% CI)	
	Unadjusted model	Adjusted model*
Diabetic retinal disease (n=27331)	1.41 (1.27 1.57)	1.37 (1.22 1.53)
Proliferative diabetic retinopathy only (n = 25970)	1.57 (1.27 1.93)	1.40 (1.12 1.74)
Diabetic macular edema only (n= 26434)	1.44 (1.26 1.65)	1.42 (1.23 1.63.)

* adjusted for age, gender, race, education, medical utilization and diabetic medication use. For the calculation of the hazard ratio of the groups with only DPR or only DME, patients with respectively DME and DPR were excluded.