Type 2 Diabetes, Glycemic Control, and Their Association With Dementia and Its Major Subtypes: Findings From the Swedish National Diabetes Register

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OBJECTIVE

Type 2 diabetes has been associated with high dementia risk. However, the links to different dementia subtypes is unclear. We examined to what extent type 2 diabetes is associated with dementia subtypes and whether such associations differed by glycemic control.

RESEARCH DESIGN AND METHODS

We used data from the Swedish National Diabetes Register and included 378,299 patients with type 2 diabetes and 1,886,022 control subjects matched for age, sex, and county randomly selected from the Swedish Total Population Register. The outcomes were incidence of Alzheimer disease, vascular dementia, and nonvascular dementia. The association of type 2 diabetes with dementia was stratified by baseline glycated hemoglobin (HbA_{1c}) in patients with type 2 diabetes only. Cox regression was used to study the excess risk of outcomes.

RESULTS

Over the follow-up (median 6.8 years), dementia developed in 11,508 (3.0%) patients with type 2 diabetes and 52,244 (2.7%) control subjects. The strongest association was observed for vascular dementia, with patients with type 2 diabetes compared with control subjects having a hazard ratio [HR] of 1.34 (95% CI 1.28, 1.41). The association of type 2 diabetes with nonvascular dementia was more modest (HR 1.10 [95% CI 1.07, 1.13]). However, risk for Alzheimer disease was lower in patients with type 2 diabetes than in control subjects (HR 0.94 [95% CI 0.90, 0.99]). When the analyses were stratified by circulating concentrations of HbA_{1c}, a dose-response association was observed.

CONCLUSIONS

The association of type 2 diabetes with dementia differs by subtypes of dementia. The strongest detrimental association is observed for vascular dementia. Moreover, patients with type 2 diabetes with poor glycemic control have an increased risk of developing vascular and nonvascular dementia.

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Although individuals with diabetes live on average 5–10 years less than those without the disease (1,2), current improvement in type 2 diabetes treatment has resulted in an incremental increase in the life expectancy of patients with type 2 diabetes (3). This increase in life expectancy means that people with type 2 diabetes will also experience a higher risk of developing other chronic diseases that are strongly associated with aging or metabolic abnormalities, such as cognitive decline and dementia (4). Recent estimates suggest that up to one-third of all dementia cases may be attributable to modifiable risk factors, including type 2 diabetes, which accounts for 3.2% of all dementia cases (5). Because diabetes prevalence rates are on the rise, it is critical to improve our understanding of the links between type 2 diabetes and dementia and its subtypes.

Evidence from prospective studies suggests that dementia risk in individuals with type 2 diabetes is 1.5–2.5 times greater than age- and sex-matched individuals without type 2 diabetes (6–8). A recent study conducted using nationwide observational registry data in 784,434 Danes age >65 years reported that individuals with diabetes have a 13% higher risk for Alzheimer disease, 98% higher risk for vascular dementia, and 53% higher risk for unspecified dementia compared with those without type 2 diabetes (6). Similarly, a large meta-analysis that pooled data from 14 prospective studies in 2.3 million participants reported that individuals with type 2 diabetes have a 60% higher risk of all-cause dementia; however, the risk was 2.3 times higher for vascular dementia and ~50% for nonvascular dementia (8).

Although several studies have reported that individuals with type 2 diabetes have a higher dementia risk (6–8), limited evidence exists regarding how much of the association between type 2 diabetes and dementia, especially subtypes of dementia, could be explained by nonmodifiable and modifiable confounding factors (6–8). There is also limited evidence on glycemic control and the risk of dementia in people with type 2 diabetes (9,10). Moreover, we do not know whether the contributions of these underlying risk factors could differ by dementia subtype. Therefore, we aimed to investigate to what extent type 2 diabetes is associated with Alzheimer disease, vascular dementia, and nonvascular dementia incidence or whether these associations differ by glycemic control and to identify what modifiable and nonmodifiable risk factors may explain the association between diabetes and dementia subtypes.

RESEARCH DESIGN AND METHODS

This study used data from the Swedish National Diabetes Register (NDR). The NDR includes ~90% of all patients aged ≥18 years diagnosed with type 2 diabetes in Sweden. Health care providers report continuously directly to the NDR or through electronic patient records from routine clinical practice. For the purposes of this report, we identified all patients with type 2 diabetes on the basis of previously validated criteria: *1*) patients aged ≥40 years at the time of diagnosis and treated with insulin only; *2*) regardless of age, patients treated with diet only or oral hypoglycemic agents combined with diet; and *3*) regardless of age, patients treated with insulin combined with oral hypoglycemic agents. This definition of type 2 diabetes has been validated against the clinician's assessment of diabetes type, which concurs in 96% of cases with no temporal differences. For each patient selected for this study, four population comparator subjects without diabetes, matched for age, sex, and county, were randomly selected from the Swedish Total Population Register. The study was approved by the regional ethical review board in Gothenburg, Sweden. All patients have given consent to inclusion in the NDR. No individual consent was required for inclusion in this study, according to Swedish law.

Outcome Data in Patients and Population Comparator Subjects

Patients and comparator subjects (hereafter referred to as control subjects) were registered from 1 January 1998 to 31 December 2012 and followed until 31 December 2013, the event of interest, or death. In brief, we used nationwide health and administrative registers in Sweden, including population registers and Statistics Sweden (vital status, demographics, socioeconomic variables), and patient registers (comorbidities, outcomes) and prescription registers (study drugs, comedications). Patients and control subjects were linked to the Swedish National Inpatient Register through their personal identification number to obtain information about coexisting health conditions, such as stroke, myocardial infarction, coronary heart diseases, heart failure, atrial fibrillation, hypertension, chronic kidney disease, cancer, gastric bypass, psychiatric disorders, and dementia subtypes.

In Sweden, ICD-10 codes are used to classify dementia, including vascular dementia (F01), nonvascular dementia (F00, F02, F03), and Alzheimer disease (G30). In this study, the diagnosis of Alzheimer disease included both early-onset and late-onset Alzheimer disease. The Swedish National Inpatient Register was used to retrieve dementia cases; this register covers nationwide-level in-hospital and hospital-based outpatient visits of all inpatient admissions from 1987 onward.

The Longitudinal Database for Health Insurance and Labor Market Studies provided information about socioeconomic variables, marital status (divided into single, married, divorced, and widowed), education level (divided into compulsory education, upper secondary, and technical or university), and country of birth (Sweden and other). The cohort has also been linked with the Swedish Prescribed Drug Register, which includes information from the entire Swedish population since 1 July 2005.

Patient phenotype and metabolic data were obtained from primary care units or hospital outpatient diabetes clinics. BMI was calculated as weight (kg)/height (m^2) from measurements taken by the reporting unit (primary care units or hospital outpatient diabetes clinics). Glycated hemoglobin (HbA_{1c}) was initially measured as percent (Mono S method) and converted into mmol/mol (International Federation of Clinical Chemistry). Microalbuminuria was defined as two positive tests from three samples taken within 1 year, with an albumin-to-creatinine ratio of 3–30 mg/mmol (~30–300 mg/g) or urinary albumin excretion rate of 20–200 μg/min (20–300 mg/L), and macroalbuminuria as albumin-to-creatinine ratio >30 mg/mmol (>300 mg/g) or urinary albumin excretion rate >200 μg/min (>300 mg/L). Triglycerides and LDL, HDL, and total cholesterol were measured in mmol/L. Systolic blood pressure was measured once or twice, and in the latter case, the mean was reported.

Smoking was self-reported by the patient at the clinic assessment unit.

Statistical Analysis

Cohort characteristics are summarized as the mean and SD for continuous variables and as frequency and percent for categorical variables for patients with type 2 diabetes matched control subjects. Standardized mean differences were estimated to compare the effect size differences between patients with type 2 diabetes and control subjects.

Incidence rates for dementia outcomes (Alzheimer disease, vascular dementia, and nonvascular dementia) were estimated as the number of events per 1,000 person-years and presented with 95% exact Poisson CIs. Cumulative incidence plots were derived using attained age (age at cohort entry) as the time scale and censoring at the first of time of the event or end of follow-up. The cumulative incidence is estimated as 1 − the survival function, which in turn is estimated based on the cumulative hazard estimated using a Nelson-Aalen estimator.

The association between type 2 diabetes (patients and matched control subjects) and dementia outcomes was investigated using Cox proportional hazards regression models with attained age as the time scale, and results are reported as hazard ratios (HRs) and 95% CIs. These analyses were adjusted for sex, income, education, country of birth, and prevalent cardiovascular disease (CVD). Competing risk analyses were conducted between all-cause death and each of the dementia outcomes fitted into the model separately. An additional competing risk analyses was conducted where all-cause death was compared with the probability of having Alzheimer disease, vascular dementia, and nonvascular dementia when all four were fitted together into the model. The cumulative incidence plots using competing risk were derived using attained age as the time scale.

To investigate whether the association between type 2 diabetes and dementia outcomes differ by glycemic control, we conducted Cox proportional hazards regression analyses by categories of HbA_{1c} concentration (<53, 53–64, 65–75, 76–86, and >86 mmol/mol). These analyses were adjusted for sociodemographics (sex, income, education, country of birth, and marital status), BMI, smoking, metabolic markers (blood pressure, lipid profile, and renal and liver function markers), medication, and existing comorbidities (including prevalent CVD). A larger number of covariates were included in these analyses because patients with type 2 diabetes go through a more detailed assessment once diabetes has been diagnosed. Trend HRs for dementia outcomes were estimated by 1-unit increments in HbA_{1c}.

To estimate the relative importance of each of these risk factors when added to a Cox proportional hazards regression model, we used Heller R^2 statistic with a gradient boosting model with a proportional hazard loss function shrinkage = 0.01, where the number of trees is optimized using fivefold cross validation. To minimize reverse causation, a 3-year landmark analysis was conducted that involved the exclusion of all dementia cases that occurred within the first 3 years since the start of the follow-up. In addition, all subjects with prevalent dementia at the index date were excluded from the analyses.

All tests were two-tailed and conducted at the 0.05 significance level. All analyses were performed using R software.

RESULTS

For this study, 378,299 patients with type 2 diabetes and 1,886,022 age- and sex-matched control subjects were included (Table 1). During the average follow-up of 7.03 years (median 6.7 years), dementia developed in 11,508 patients with type 2 diabetes (2,320 Alzheimer disease, 2,155 vascular dementia, and 7,033 nonvascular dementia) compared with 52,244 control subjects (12,834 Alzheimer disease, 7,629 vascular dementia, and 31,781 nonvascular dementia).

The cohort characteristics for type 2 diabetes and control are presented in Table 1. In summary, the mean age for both groups was 64 years, and 55% were men. Patients with type 2 diabetes had lower income and lower education levels than control subjects. A higher prevalence of hospital admissions for CVDs, hypertension, cancer, and gastric bypass was observed in patients with type 2 diabetes compared with control subjects. Cohort characteristics by HbA_{1c} level are presented in Supplementary Table 1.

Compared with control subjects without diabetes, patients with type 2 diabetes had a 34% higher risk for vascular dementia (HR 1.34 [95% CI 1.28, 1.41]) and 10% higher risk of nonvascular dementia (HR 1.10 [95% CI 1.07, 1.13]) independent of sex, income, education, country of birth, and existing CVD (Table 2). The risk for Alzheimer disease was 6% lower in patients with type 2 diabetes than in control subjects (HR 0.94 [95% CI 0.90, 0.99]) (Table 2). When competing risk analyses including Alzheimer disease, vascular dementia, nonvascular dementia, and all-cause mortality were performed using a cumulative incidence plot, we observed that patients with type 2 diabetes died earlier than control subjects, which reduced the probability of Alzheimer disease developing in patients with type 2 diabetes compared with control subjects (Fig. 1).

The association between HbA_{1c} concentration and risk of dementia and its subtypes in patients with type 2 diabetes are presented in Table 3. Although a linear association was found between HbA_{1c} concentration and dementia risk, the magnitude of the association differed by subtype of dementia. The strongest association was observed for vascular dementia; compared with patients with HbA_{1c} <53 mmol/mol, those with HbA_{1c} ≥87 mmol/mol had a 93% higher risk (HR 1.93 [95% CI 1.54, 2.43]). A slightly lower risk was observed for nonvascular dementia (HR 1.67 [95% CI 1.46, 1.91]) and Alzheimer disease (HR 1.35 [95% CI 1.04, 1.75]) between these patient subtypes (Table 3). These associations were independent of BMI, metabolic biomarkers, education, country of birth, marital status, and prevalent CVD. When the analyses were conducted using a 3-year landmark analysis, the magnitude of the associations was slightly attenuated, but dose-response was maintained for vascular and nonvascular dementia and disappeared for Alzheimer disease (Table 3). The accumulative incidence of dementia subtypes by categories of HbA_{1c} concentration are presented in Supplementary Fig. 2.

Among patients with type 2 diabetes, the modifiable and nonmodifiable risk factors that accounted for most of the association with dementia outcomes are presented in Table 4. Age was the main risk factor for dementia with a relative influence of 74.5%, 81.7%, and 81.7% for Alzheimer disease, nonvascular dementia,

Table 1—Cohort characteristics

Variable	Control	Type 2 diabetes	*P*	SMD
Subjects, *n*	1,886,022	378,299		
Sociodemographics				
Age, years	64.07 (12.31)	64.13 (12.33)	0.016	0.004
Male sex	1,032,957 (54.8)	206,970 (54.7)	0.511	0.001
Income, hundreds of SEK	2,071.3 (4474.5)	1,767.8 (2538.5)	<0.001	0.083
Education			<0.001	0.223
Primary	635,087 (34.2)	153,559 (41.5)		
Secondary	753,329 (40.5)	154,553 (41.7)		
College/university	470,455 (25.3)	62,110 (16.8)		
Marital status			<0.001	0.046
Married	1,056,801 (63.7)	202,038 (61.5)		
Separated	307,279 (18.5)	65,054 (19.8)		
Single	295,243 (17.8)	61,396 (18.7)		
Widowed	68 (0.0)	5 (0.0)		
Health-related variables				
Duration of diabetes, years	NA	5.12 (6.79)	NA	NA
HbA_{1c}	NA	53.99 (14.86)	NA	NA
BMI, kg/m^2	NA	30.00 (5.45)	NA	NA
Systolic blood pressure, mmHg	NA	138.94 (17.75)	NA	NA
Diastolic blood pressure, mmHg	NA	78.61 (9.88)	NA	NA
LDL cholesterol, mmol/L	NA	2.95 (0.97)	NA	NA
HDL cholesterol, mmol/L	NA	1.27 (0.39)	NA	NA
Triglycerides, mmol/L	NA	1.93 (1.24)	NA	NA
GFR, mL/min/1.73 m^2	NA	81.37 (25.13)	NA	NA
Macroalbuminuria	NA	16,542 (6.6)	NA	NA
Microalbuminuria	NA	33,014 (15.8)	NA	NA
Smoker	NA	50,046 (16.8)	NA	NA
Prevalent health conditions				
Coronary heart disease	149,682 (7.9)	62,111 (16.4)	<0.001	0.262
Myocardial infarction	74,149 (3.9)	32,954 (8.7)	<0.001	0.197
Stroke	66,749 (3.5)	22,936 (6.1)	<0.001	0.118
Heart failure	47,693 (2.5)	22,228 (5.9)	<0.001	0.167
Atrial fibrillation	81,953 (4.3)	26,674 (7.1)	<0.001	0.117
Renal disease	2,240 (0.1)	803 (0.2)	<0.001	0.023
Hypertension	294 (0.0)	4,599 (1.2)	<0.001	0.154
Pre-index amputation	1,409 (0.1)	1,287 (0.3)	<0.001	0.058
Cancer	124,429 (6.6)	27,326 (7.2)	<0.001	0.025
Psychiatric disorders	36,179 (1.9)	12,169 (3.2)	<0.001	0.082
Gastric bypass	587 (0.0)	310 (0.1)	<0.001	0.021
Types of diabetes treatment			NA	NA
Diet only	NA	145,694 (38.5)		
Oral antidiabetic drug	NA	166,173 (43.9)		
Insulin	NA	32,277 (8.5)		
Insulin + oral antidiabetic drug	NA	34,155 (9.0)		

Data are mean (SD) for continuous variables and *n* (%) for categorical variables. Note that prevalent health condition data are based on percentage with prior hospitalizations for specific conditions. GFR, glomerular filtration rate; NA, not available; SMD, standardized mean difference.

and vascular dementia, respectively. However, the relative influence of other risk factors differed by dementia subtype. For vascular dementia, the risk factors with the greatest relative influence were diastolic blood pressure (13.4%), systolic blood pressure (7.8%), years with diabetes (7.4%), existing CVD (5.7%), BMI (5.0%), and glomerular filtration rate (4.5%). Other factors such as HbA_{1c}, income, HDL cholesterol, LDL cholesterol, macro- and microalbuminuria, smoking, lipids medication, and education explained <2% each. For nonvascular dementia, the top risk factors after age (81.7%) were BMI (5.4%) and years with diabetes (2.0%). Other factors such as blood pressure, glomerular filtration rate, CVD, HbA_{1c}, and sociodemographic factors explained <2% each. For Alzheimer disease, age (74.5%), BMI (13.7%), and systolic blood pressure (4.9%) were the main risk factors (Table 4).

CONCLUSIONS

The main findings provide evidence that individuals with type 2 diabetes have a higher risk of vascular and nonvascular dementia, and the risk is greater for vascular dementia than nonvascular dementia. Risk of Alzheimer disease was lower among patients with type 2 diabetes, which could be explained by competing risk, as those with type 2 diabetes died earlier than their counterparts without type 2 diabetes, reducing

Table 2—Association between diabetes and risk of dementia subtypes

Outcome	HR (95% CI)	*P*	Events	Person-years	Incidence rate (95% CI)
Alzheimer disease					
Control	1.00 (Ref)		12,834	10,409,681	1.23 (1.21, 1.25)
Type 2 diabetes	0.94 (0.90, 0.99)	0.011	2,320	2,044,254	1.13 (1.09, 1.18)
Vascular dementia					
Control	1.00 (Ref)		7,629	10,420,918	0.73 (0.72, 0.75)
Type 2 diabetes	1.34 (1.28, 1.41)	<0.0001	2,155	2,044,675	1.05 (1.01, 1.10)
Nonvascular dementia					
Control	1.00 (Ref)		31,781	10,382,823	3.06 (3.03, 3.09)
Type 2 diabetes	1.10 (1.07, 1.13)	<0.0001	7,033	2,037,488	3.45 (3.37, 3.53)

HRs were adjusted for sex, income, education, country of birth, and prevalent CVD. Number of events, person-years, and incidence rate are per 1,000 person-years with exact 95% Poisson CI. Ref, reference group.

the risk of developing Alzheimer disease. Our findings also provide evidence that within individuals with type 2 diabetes, poor glycemic control is associated with an elevated risk of dementia but only for vascular dementia and nonvascular dementia; no clear associations were identified for Alzheimer disease, as the association was fully attenuated and no longer significant when a 3-year landmark analysis was applied. Although several underlying risk factors could explain the higher risk of dementia observed in patients with type 2 diabetes, we identified that the relative influence of these factors differs by subtypes of dementia. Years with diabetes, BMI, existing CVD, and blood pressure were identified as some of the key factors explaining the association between type 2 diabetes and dementia risk. These findings are of important public health relevance because BMI and blood pressure are modifiable risk factors, as is diabetes per se; therefore, identification of high-risk individuals and tailored interventions or treatment could attenuate the dementia risk attributable to type 2 diabetes.

Our findings partially corroborate previous evidence suggesting that type 2 diabetes is a risk factor for dementia and that this risk differs by subtypes of dementia (6–8). A large meta-analysis that pooled data from 14 prospective studies in 2.3 million participants and >100,000 cases of dementia (8) reported that individuals with type 2 diabetes have a 60% higher risk of all-cause dementia and 40% risk for nonvascular dementia for both men and women. However, the risk of vascular dementia in patients with type 2 diabetes was 19% higher in women than in men. Similarly, another study conducted using Danish nationwide observational registry data (6) from 784,434 individuals aged >65 years reported that those with type 2 diabetes had a 13% higher risk for Alzheimer disease, 53% higher risk for unspecified dementia, and 98% higher risk for vascular dementia than those without diabetes (6). Although our findings broadly agree with these studies, our risk estimate for vascular and nonvascular dementia subtypes in patients with type 2 diabetes were slightly lower perhaps because we better matched for age, sex, and area of residence. In contrast to the study conducted using the Danish register (6), we found an inverse association between type 2 diabetes and Alzheimer disease. Evidence regarding the association between diabetes and Alzheimer disease is controversial, with some studies reporting a higher risk in patients with type 2 diabetes and others reporting a lack of association (11,12). Differences in the direction of the association could be explained by unmeasured confounding factors, as evidence from Mendelian randomization studies has reported no association between diabetes and Alzheimer disease (6,13). Our findings also suggest that the lower risk of Alzheimer disease observed in patients with type 2 diabetes could be attributable to competing risk, as individuals without type 2 diabetes live longer than those with type 2 diabetes, which makes them more likely to develop Alzheimer disease.

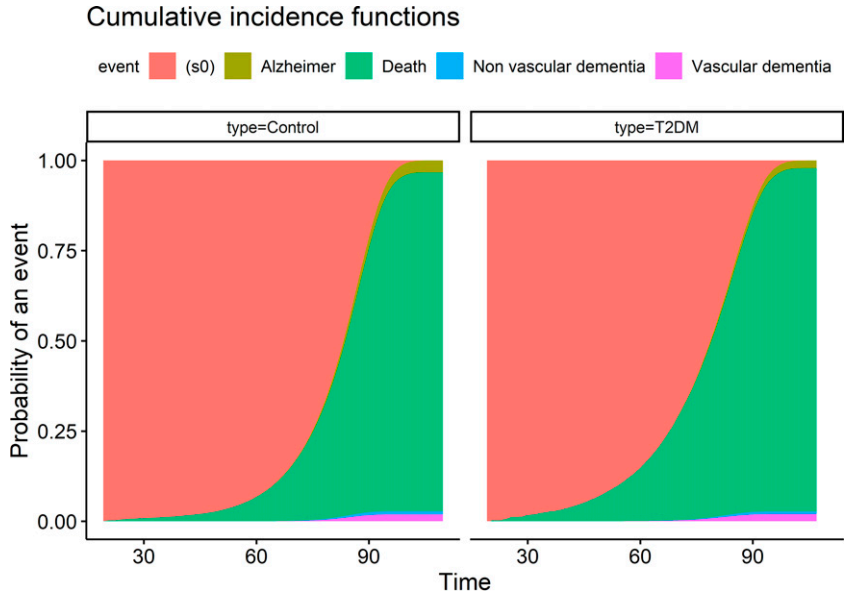

Figure 1—Cumulative incidence using competing risk analysis between Alzheimer disease, vascular dementia, and nonvascular dementia and all-cause mortality. Attained age was used as the time scale. (s0), participants without any of the four outcomes fitted into the competing risk analysis; T2DM, type 2 diabetes mellitus.

Table 3—Association between HbA_{1c} concentration and risk of dementia subtypes in patients with type 2 diabetes

Outcome	HbA_{1c} (mmol/mol)	HR (95% CI)	*P*	Landmark HR (95% CI)*	*P*
Alzheimer disease	≤52	1.00 (Ref)		1.00 (Ref)	
	53–64	1.02 (0.92, 1.12)	0.741	1.09 (0.97, 1.23)	0.141
	65–75	1.08 (0.94, 1.25)	0.293	1.07 (0.89, 1.28)	0.471
	76–86	1.32 (1.06, 1.65)	0.013	1.38 (1.05, 1.81)	0.021
	≥87	1.35 (1.04, 1.75)	0.026	1.24 (0.86, 1.77)	0.249
Trend		1.004 (1.001, 1.008)	0.009	1.005 (1.001, 1.009)	0.008
Vascular dementia	≤52	1.00 (Ref)		1.00 (Ref)	
	53–64	1.18 (1.07, 1.31)	0.001	1.16 (1.02, 1.32)	0.022
	65–75	1.40 (1.22, 1.61)	<0.0001	1.46 (1.23, 1.73)	<0.0001
	76–86	1.75 (1.43, 2.14)	<0.0001	1.76 (1.36, 2.27)	<0.0001
	≥87	1.93 (1.54, 2.43)	<0.0001	1.92 (1.41, 2.60)	<0.0001
Trend		1.01 (1.01, 1.02)	<0.0001	1.01 (1.01, 1.02)	<0.0001
Nonvascular dementia	≤52	1.00 (Ref)	0.011	1.00 (Ref)	
	53–64	1.10 (1.04, 1.16)	0.0009	1.15 (1.07, 1.23)	0.0001
	65–75	1.32 (1.22, 1.42)	<0.0001	1.28 (1.17, 1.41)	<0.0001
	76–86	1.46 (1.30, 1.65)	<0.0001	1.41 (1.21, 1.65)	<0.0001
	≥87	1.67 (1.46, 1.91)	<0.0001	1.61 (1.35, 1.93)	<0.0001
Trend		1.009 (1.007, 1.011)	<0.0001	1.009 (1.007, 1.011)	<0.0001

The reference (Ref) group included patients with an HbA_{1c} <53 mmol/mol. The analyses were adjusted for age, sex, marital status, income, education, smoking, BMI, number of years with type 2 diabetes, diastolic and systolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, estimated glomerular filtration rate, macro- and microalbuminuria, medication for blood pressure, lipids, and prevalent CVD. *Conducted using a 3-year landmark analysis. HR for trend was estimated per 1-unit (mmol/mol) increment in HbA_{1c}.

Evidence regarding the role of glycemic control on the association between type 2 diabetes and dementia risk is limited and not fully understood (9,10). A study conducted in two cohorts (Glostrup and ADDITION [Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care] cohorts), which included >16,000 and 25,000 individuals, respectively, found that HbA_{1c} levels >48 mmol/mol were associated with a higher risk of dementia in the Glostrup cohort (HR 1.94 [95% CI 1.10, 3.44]), but no such association was observed for the ADDITION cohort (HR 0.96 [95% CI 0.57, 1.61]) (14). Two previous studies found that HbA_{1c} of >53 mmol/mol was associated with a higher risk of dementia. In contrast, a diagnosis of diabetes or self-reported diabetes was not associated with dementia risk (15,16). However, these studies only had 58 and 67 patients with dementia, respectively. The major limitations of previous studies have been not only their limited sample size but also their lack of a dose-response association analysis, which included a higher number of groups on the basis of HbA_{1c} concentration. Our study provides, therefore, novel evidence regarding a dose-response association between HbA_{1c} concentration and dementia risk in patients with type 2 diabetes. We observed that compared with patients with type 2 diabetes with better glycemic control, those with levels >53 mmol/mol for HbA_{1c} have a higher risk of vascular and nonvascular dementia, with risk increasing on average by 1.3% and 0.9% per 1 mmol/mol higher HbA_{1c}, respectively.

Moreover, no previous studies have explored what risk factors could partly explain the high dementia risk observed in individuals with type 2 diabetes. Although age is the main factor behind this association, other modifiable risk factors could contribute to this excess risk. However, the relative contribution of these factors varies by subtype of dementia. Blood pressure and BMI are two of the main modifiable risk factors that could be targeted in future interventions aiming to reduce the risk of dementia in patients with type 2 diabetes, with prevention of diabetes in people at elevated risk also likely to be beneficial. Our findings, therefore, have important clinical implications. If 1 in 10–15 cases of dementia are attributable to type 2 diabetes, diabetes prevention and risk factor management become potential targets for dementia prevention (17). Although type 2 diabetes is considered a chronic disease, results from the Diabetes Remission Clinical Trial (DiRECT) provide strong evidence for the potential of weight loss on the remission of type 2 diabetes, at least for a period of time (18). DiRECT showed that almost one-half of participants achieved remission to a nondiabetic state and came off antidiabetic drugs after weight loss; therefore, remission of type 2 diabetes is a realistic target for primary care (18) and could help to lessen dementia risks.

There are several strengths of this study: *1*) the large sample of individuals with type 2 diabetes in whom dementia developed during the 7-year follow-up, *2*) the prospective approach and capacity to reflect usage in a real-world setting, and *3*) the register-based study design, which provided detailed data on dementia outcomes beyond all-cause dementia, existing major comorbidities, socioeconomic status, and laboratory-measurable risk factors. However, some limitations should be considered when interpreting our findings. In an observational study, a possibility always exists for residual confounding due to unmeasured variables; for example, hereditary factors and comorbidities such as psychiatric disease could influence both the

Table 4—Relative influence of modifiable and nonmodifiable risk factors on the association between type 2 diabetes and dementia risk

Alzheimer disease	RI, %	Vascular dementia	RI, %	Nonvascular dementia	RI, %
Age	74.5	Age	47.84	Age	81.71
BMI	13.7	Diastolic blood pressure	13.46	BMI	5.48
Systolic blood pressure	4.91	Systolic blood pressure	7.84	Type 2 diabetes duration	2.32
Type 2 diabetes duration	1.45	Type 2 diabetes duration	7.47	Diastolic blood pressure	1.70
Income	1.30	CVD	5.76	Glomerular filtration rate	1.60
Glomerular filtration rate	1.04	BMI	5.07	Systolic blood pressure	1.51
HDL	1.22	Glomerular filtration rate	4.52	CVD	1.49
LDL	0.86	LDL	2.44	HbA_{1c}	1.06
Diastolic blood pressure	0.49	HbA_{1c}	1.78	Income	1.00
HbA_{1c}	0.32	Income	0.95	LDL	0.54
Education	0.23	Macroalbuminuria	0.94	HDL	0.38
Microalbuminuria	0.10	HDL	0.77	Macroalbuminuria	0.35
Blood pressure medication	0.05	Male sex	0.62	Lipid medication	0.34
Male sex	0.02	Microalbuminuria	0.28	Blood pressure medication	0.21
Smoking	0.02	Smoking	0.18	Microalbuminuria	0.15
Lipid medication	0.002	Lipid medication	0.08	Education	0.09
Macroalbuminuria	0.004	Education	0.01	Smoking	0.05

Analyses were mutually adjusted for all covariates. RI, relative influence.

exposure and the outcome. Because of the nature of the diabetes register, important confounding factors are not collected or measured routinely in primary care and hospital settings, such as physical activity, alcohol intake, and dietary variables, which could also explain part of the association between diabetes and dementia risk. Although our analyses were conducted using a 3-year landmark analysis and excluded individuals with dementia at the start of follow-up, we cannot fully remove the effect of reverse causation. Finally, we accept that the ICD-10 code used for diagnosing dementia is more limited than the DSM-IV criteria because ICD-10 lacks information on cognitive tests used and symptoms recorded.

Our study corroborates that type 2 diabetes is a risk factor for vascular dementia; however, the lower risk of Alzheimer disease observed in patients with type 2 diabetes may be attributable to competing risk, especially if these individuals do not live long enough for this condition to develop. Our findings extend limited evidence that suggests that poor glycemic control is associated with a higher risk of dementia in a dose-response manner, primarily vascular and nonvascular dementia. We also provide novel evidence regarding the underlying factors that may contribute to the association between type 2 diabetes and dementia risk, which could help to inform future interventions aiming to develop targeted interventions or treatment for high-risk individuals. Considering that both type 2 diabetes and dementia are linked chronic diseases with a substantial personal and economic burden worldwide, our findings hold important public health relevance.

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Author Contributions. C.A.C.-M. and N.S. wrote the manuscript. S.F. and E.N. performed the data cleaning and statistical analysis of the data. K.E.-O., A.-M.S., S.G., and B.E. were involved in data acquisition. S.G., B.E., and N.S. conceived and designed the study. All authors contributed to the interpretation of the data and critical revision of the manuscript for important intellectual content and approved the final draft. B.E. and N.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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