Glycemic Control, Diabetic Complications, and Risk of Dementia in Patients With Diabetes: Results From a Large U.K. Cohort Study

Bang Zheng,[1] Bowen Su,[2] Geraint Price,[1] Ioanna Tzoulaki,[2] Sara Ahmadi-Abhari,[1] and Lefkos Middleton[1,3]

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OBJECTIVE

Type 2 diabetes is an established risk factor for dementia. However, the roles of glycemic control and diabetic complications in the development of dementia have been less well substantiated. This large-scale cohort study aims to examine associations of longitudinal HbA_{1c} levels and diabetic complications with the risk of dementia incidence among patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Data of eligible patients with diabetes, aged ≥50 years in the U.K. Clinical Practice Research Datalink from 1987 to 2018, were analyzed. Time-varying Cox regressions were used to estimate adjusted hazard ratios (HRs) and 95% CIs for dementia risk.

RESULTS

Among 457,902 patients with diabetes, 28,627 (6.3%) incident dementia cases were observed during a median of 6 years' follow-up. Patients with recorded hypoglycemic events or microvascular complications were at higher risk of dementia incidence compared with those without such complications (HR 1.30 [95% CI 1.22–1.39] and 1.10 [1.06–1.14], respectively). The HbA_{1c} level, modeled as a time-varying exposure, was associated with increased dementia risk (HR 1.08 [95% CI 1.07–1.09] per 1% HbA_{1c} increment) among 372,287 patients with diabetes with postdiagnosis HbA_{1c} records. Similarly, a higher coefficient of variation of HbA_{1c} during the initial 3 years of follow-up was associated with higher subsequent dementia risk (HR 1.03 [95% CI 1.01–1.04] per 1-SD increment).

CONCLUSIONS

Higher or unstable HbA_{1c} levels and the presence of diabetic complications in patients with type 2 diabetes are associated with increased dementia risk. Effective management of glycemia might have a significant role in maintaining cognitive health among older adults with diabetes.

The number of older adults living with Alzheimer disease (AD) and other forms of late-onset dementia (LOD) is increasing exponentially, in parallel with increases in life expectancy and population ageing, across the globe (1,2). Type

[1]Ageing Epidemiology Research Unit, School of Public Health, Imperial College London, London, U.K.
[2]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, U.K.
[3]Public Health Directorate, Imperial College Healthcare NHS Trust, London, U.K.

Corresponding author: Lefkos Middleton, l.middleton@imperial.ac.uk

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2 diabetes is another highly prevalent chronic disease in late life and is a well-established risk factor for dementia (3). Three meta-analyses of previous cohort studies showed a 53–73% higher risk of LOD or AD in patients with diabetes compared with subjects without diabetes (4–6). Furthermore, several reports have linked type 2 diabetes with the presence of specific AD biomarkers, such as cerebrospinal fluid phosphorylated tau and total tau (7), reduced brain volume, and fluorodeoxyglucose uptake (7,8).

Most previous epidemiological studies mainly focused on defining the increased risk of dementia associated with diagnosis or presence of diabetes. However, the biological mechanisms underlying this relationship and the role of glycemic control and diabetic complications in dementia development are less well understood (9,10). Reports on plasma glucose or glycosylated hemoglobin A_{1c} (HbA_{1c}) levels and cognitive outcomes had contradictory results (11–14), probably limited by relatively small sample sizes, variable length of follow-up, or reverse causality bias. Of note, HbA_{1c} variability, an important indicator of long-term control of diabetes, has recently been found to be positively associated with micro- and macrovascular complications and mortality in patients with diabetes, independently of HbA_{1c} levels (15). The effect of HbA_{1c} variability on dementia risk is less clear.

With regard to diabetic complications, extensive evidence suggests that hypoglycemia, a common acute complication of diabetes treatment, is associated with adverse cognitive outcomes among older adults (16–18). In contrast, other prevalent diabetic complications resulting from microvascular lesions, such as diabetic retinopathy, nephropathy, and neuropathy, have drawn less attention with respect to dementia risk.

Our study aims to comprehensively evaluate the associations of longitudinal HbA_{1c} levels and their long-term variability, as well as of diabetic complications, with dementia incidence in a large cohort of older patients with type 2 diabetes, leveraging electronic health record (EHR) data from the U.K. Clinical Practice Research Datalink (CPRD) (19).

RESEARCH DESIGN AND METHODS

Data Sources

The U.K. CPRD GOLD database is a primary care database that includes ongoing longitudinal collection of fully coded EHRs of >17 million individuals who are (or were) registered with >700 participating general practitioner (GP) practices in the U.K. (19). The available data include symptomatology, clinical diagnosis, results of investigations, prescriptions, secondary care referrals, and vaccinations. CPRD was linked to secondary care data, such as the Hospital Episode Statistics (HES), mortality data from the Office for National Statistics (ONS), and regional data on measures of social deprivation. The demographic profiles of the patient population in CPRD are similar to those of the general population of the U.K. (19).

Study Population

Individual-level data between 1987 and 2018 were extracted for this study. Patients were included if they were aged ≥50 years at any point during their CPRD registration period and had a diagnosis of diabetes, based on relevant CPRD Medcode or a prescription of antidiabetes drugs (oral hypoglycemic agents or insulin) (Supplementary Table 1). In addition, eligible participants were required to have been registered in CPRD for at least 1 year prior to diabetes onset to ensure that the date of newly diagnosed diabetes was captured and to allow time for baseline information to be recorded. Patients with a diagnosis of type 1 diabetes or those who had a diagnosis of diabetes or initiation of treatment prior to 30 years of age were excluded. Patients were also excluded if they had a diagnosis of dementia before cohort entry. To account for reverse causality bias (i.e., that prodromal cognitive/functional impairment prior to dementia diagnosis could result in poorer management of diabetes), those who developed dementia or died during the first 2 years after cohort entry or the onset of diabetic complication were excluded from the analyses of diabetic complications and dementia risk; those who developed dementia or died during the first 2 years following the first post–diabetes diagnosis HbA_{1c} record after 50 years of age were excluded from the analyses of HbA_{1c} levels and dementia risk.

A total of 457,902 individuals fulfilled the inclusion and exclusion criteria and were included in the analysis on diabetic complications and dementia risk. Among these participants, 372,287 individuals had at least one HbA_{1c} record at ≥50 years of age and post–diabetes diagnosis and were included in the analysis of longitudinal HbA_{1c} levels and dementia risk.

Exposure Assessment

Episode of hypoglycemia, microvascular diabetic complications such as nephropathy, retinopathy, and neuropathy (including diabetic foot), and other complication events (such as coma, ulcer, and unspecified records of diabetic complications) were extracted using the corresponding CPRD Medcode (Supplementary Table 2). To comprehensively identify hypoglycemia episodes, we used codes of severe hypoglycemia, hospital-treated hypoglycemia, hypoglycemia without coma, and unspecified hypoglycemia (17). The date of onset of a specific type of complication was defined according to its first relevant health record. The date of onset of overall microvascular complications was defined as the earliest date of developing nephropathy, retinopathy, or neuropathy.

Longitudinal HbA_{1c} concentrations were recorded as test results and extracted using CPRD Medcode and Enttype code (Supplementary Table 3). The HbA_{1c} value, measured as a continuous variable, was also stratified into different clinically established categories (<6%, 6–7%, 7–8%, 8–9%, 9–10%, and ≥10%). For patients with at least three HbA_{1c} records during the first 3 years of follow-up, mean and coefficient of variation (CV; the ratio of the SD to the mean) of the 3-year HbA_{1c} measurements were estimated and assessed as additional exposure variables, reflecting the average level and variability of long-term HbA_{1c} concentrations.

In addition, information on the following covariates was extracted: age at cohort entry, sex, calendar year of cohort entry, region in U.K., index of multiple deprivation (IMD; a proxy of socioeconomic status linked to CPRD), BMI (latest record up to 10 years before cohort entry to reduce missing values), smoking status (latest record up to 5

years before cohort entry), duration of diabetes at cohort entry (based on the first clinical record of diabetes diagnosis), history of antidiabetes treatment, and history of major comorbidities, including chronic heart disease, stroke, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, and cancer.

Outcome Ascertainment

The outcome event was dementia incidence. We did not distinguish by specific LOD type, as such granular level of data are variably registered in CPRD, and the precision of health data recording varies over time. Moreover, it is acknowledged that most cases of LOD involve mixed brain pathologies (20,21). Patients were considered to have dementia if they: *1*) had a dementia diagnosis based on Medcode in CPRD; *2*) had a dementia diagnosis based on ICD codes in linked HES or ONS databases; or *3*) had at least one dementia-specific drug prescription (donepezil, galantamine, rivastigmine, or memantine [22]) (Supplementary Table 4). Patients with dementia with diagnoses of unrelated etiologies, such as following HIV infection, Creutzfeldt-Jakob disease, or alcohol- and drug-induced, were excluded. Among the extracted subjects with dementia, 96% were based on diagnosis code, and 4% were based on dementia-specific drug prescription. The outcome event date was defined as the first dementia diagnosis date or the first prescription date of dementia-specific drugs, whichever occurred earlier.

Statistical Analysis

Distributions of baseline characteristics were summarized and compared between subcohort patients with baseline HbA_{1c} levels $<$7% (53 mmol/mol) and $\geq$7%. Time-varying Cox proportional hazards models, with age as the underlying time-scale, were used to estimate hazard ratios (HRs) and 95% CIs of dementia associated with diabetic complications or longitudinal HbA_{1c} levels in separate analyses. Exposures were treated as time-varying variables.

In analyses of diabetic complications, the presence of hypoglycemic episodes and microvascular complications in aggregate and by type (nephropathy, retinopathy, and neuropathy) in association with dementia incidence were examined in separate Cox models. Patients who developed a relevant diabetic complication during follow-up contributed person-years to the no-complication group up until the complication diagnosis date and then contributed person-years to the complication group. Time of cohort entry for each patient was defined as date of diabetes onset, aged 50 or 1 January 1987, whichever was the latest. The end of follow-up was defined as date of dementia incidence, death, transfer-out date, last data collection date of GP practice, or 1 May 2018, whichever occurred first. The patient-level transfer-out date recorded in CPRD refers to the date the patient transferred out of the practice. The practice-level last data collection date refers to the date of the latest data upload from each GP practice (19). To examine independent effects of different types of microvascular complications, an additional analysis mutually adjusting for nephropathy, retinopathy, and neuropathy was conducted.

For the analysis of longitudinal HbA_{1c} level, given that glycemic levels change over time for each patient with diabetes, the time-varying Cox model was used to estimate the HR and 95% CI of dementia incidence per 1% increment (absolute value) of HbA_{1c} among patients with at least one HbA_{1c} record post–diabetes diagnosis after 50 years of age. In a separate Cox model, time-varying HbA_{1c} category ($<$6%, 6–7%, 7–8%, 8–9%, 9–10%, and $\geq$10%) was assessed as the exposure variable to explore the potential nonlinear relationship with dementia risk, with 6–7% as reference group. The beginning of follow-up for this cohort was defined as date of the first postdiagnosis HbA_{1c} record after 50 years of age (i.e., baseline HbA_{1c}). The end of follow-up was defined as above. To account for reverse causality bias, HbA_{1c} concentrations recorded within 2 years prior to dementia incidence or death were excluded.

For the analysis of long-term average level of HbA_{1c} and its variability, the 3-year mean and CV of HbA_{1c} were simultaneously entered into a conventional Cox model to estimate their independent associations with dementia incidence. Follow-up time for this analysis was calculated from 3 years after the baseline HbA_{1c} record (to avoid concurrent bias), until the date of dementia incidence or censoring time. Patients who developed dementia or died during the first 2 years of follow-up were excluded. In addition, mean and CV of HbA_{1c} were both modeled as categorical variables ($<$6%, 6–7%, 7–8%, 8–9%, 9–10%, and $\geq$10% for mean value; quartiles for CV) in a separate Cox model.

To account for potential confounding factors, three sequential models with increasing levels of adjustment for covariates were created for all analyses: model 1 adjusted for age, sex, calendar year, and region; model 2 further adjusted for IMD (in quintile), smoking status (nonsmoker, current smoker, ex-smoker, or missing), BMI category ($<$25, 25–30, and $\geq$30 kg/m^2 or missing), and history of comorbidities; and model 3 additionally adjusted for diabetes-related factors, including duration of diabetes, presence of diabetic complications (only for HbA_{1c} analysis), baseline HbA_{1c} level (only for diabetic complications analysis), and prescription of antidiabetes drugs (no drug, only oral hypoglycemic drug, or insulin). Covariates were also modeled as time-varying variables and updated at complication diagnosis date or each HbA_{1c} record date during follow-up. Missing values in smoking status and BMI category during follow-up were imputed with last observation carried forward.

We further repeated the main analyses in males and females separately and tested the effect modification by sex. Several sensitivity analyses were conducted to assess the robustness of our findings: *1*) restricting to participants who were at least 60 years old at cohort entry; *2*) restricting to those who were at least 80 years old at the end of follow-up to account for the competing risk of premature death, in which the estimated HR reflects relative hazard of dementia conditional on patients surviving beyond 80 years of age; *3*) restricting to participants who entered cohort after 2004, as diabetes data quality was significantly improved in CPRD following the introduction of the Quality and Outcomes Framework indicators for diabetes, and to account for the change of clinical practice and guidelines of diabetes management over time (23); *4*) not excluding HbA_{1c} recorded within 2 years prior to dementia incidence or death in the analysis of longitudinal HbA_{1c}; *5*)

excluding HbA_{1c} records within 5 years prior to dementia incidence or patients who developed dementia within the first 5 years of follow-up to further reduce reverse causality; *6*) excluding possible outlier values in HbA_{1c} records ($<$4% or $>$12%); *7*) adjusting the 3-year CV of HbA_{1c} for the possible influence of number of HbA_{1c} records (24) (adjusted CV = CV/[total records during 3-year follow-up/total records during 3-year follow-up $-$ 1]$^{1/2}$) and also stratifying the analysis by the median number of HbA_{1c} records; *8*) additionally adjusting for the average number of clinical visits per year during follow-up of each patient, since patients who visited a GP more frequently may have a systematically different profile or higher diagnosis rate; *9*) additionally adjusting for the identifier of GP practices to account for the practice group variability; and *10*) using a more stringent dementia ascertainment criterion that requires at least two dementia diagnosis records within or between data sources or at least one dementia diagnosis record plus one dementia-specific drug prescription (25).

The statistical analyses were performed using Stata (version 15; Stata Corp.). All statistical tests were two-sided, and the significance level was defined as $P < 0.05$.

Data and Resource Availability

This study is based on data from the CPRD obtained under license from the U.K. Medicines and Healthcare Products Regulatory Agency (protocol approved by the Independent Scientific Advisory Committee, number 19_065R). According to the U.K. Data Protection Act, information governance restrictions (to protect patient confidentiality) prevent data sharing via public deposition. Data extracts can be requested by applying to the CPRD (https://www.cprd.com).

RESULTS

Baseline Characteristics of Study Population

Of the 457,902 patients with type 2 diabetes, 52.1% were male; the mean baseline age was 64.5 (SD 10.8) years (Table 1). At cohort entry, 42.3% of patients had obesity (BMI $\geq$30 kg/m^2), and 19.0% were self-reported current smokers; 17.1% had been prescribed antidiabetes drugs, and the mean baseline HbA_{1c} level was 7.4% (57 mmol/mol) (SD 2.1%). Prior to baseline, only 1,986 (0.4%) patients had hypoglycemic events, and 8,060 (1.8%) had microvascular complications (5,928 subjects with retinopathy, 2,275 with neuropathy, and 569 with nephropathy). During follow-up, 17,524 (3.8%) patients developed hypoglycemic episodes, and 103,188 (22.5%) patients developed microvascular complications (73,615 with retinopathy, 41,920 with neuropathy, and 8,660 with nephropathy).

Among the 372,287 patients included in analyses on longitudinal HbA_{1c}, 216,600 (58.2%) had HbA_{1c} levels $<$7% (53 mmol/mol) at baseline (Table 1). Compared with patients with HbA_{1c} $<$7%, those with HbA_{1c} $\geq$7% were slightly younger, entered the cohort earlier, presented with less comorbidities, and were more likely to be male, deprived, obese ,and current smokers; they also had a longer duration of diabetes and higher proportion of antidiabetes drug use and diabetic complications before baseline ($P < 0.05$). Patients with post–diabetes diagnosis HbA_{1c} record were slightly more likely to have obesity, chronic heart disease, and hypertension at baseline than those without (Supplementary Table 5).

Diabetic Complications in Association With Dementia Risk

During a median of 6 years' follow-up (ranging from 0–31 years) of the 457,902 patients with diabetes, 28,627 (6.3%) incident dementia cases were recorded. After adjusting for a full set of covariates (model 3), there was evidence for an association between hypoglycemic events and a higher risk of dementia incidence (HR 1.30 [95% CI 1.22–1.39]) (Table 2). The HR estimates were 1.50 in model 1 and 1.44 in model 2 ($P < 0.05$).

Microvascular complications were also associated with a higher risk of dementia incidence in the fully adjusted model (HR 1.10 [95% CI 1.06–1.14]) as well as in models 1 and 2 (HR 1.22 and 1.21, respectively). Neuropathy and nephropathy had relatively stronger association with dementia incidence (HR 1.25 [95% CI 1.18–1.33] and 1.23 [1.13–1.33]; model 3) than retinopathy (HR 1.07 [95% CI 1.03–1.11]; model 3). The analysis mutually adjusting for neuropathy, nephropathy, and retinopathy revealed similar results; the HRs were 1.25 (95% CI 1.18–1.33), 1.24 (95% CI 1.14–1.35), and 1.06 (95% CI 1.02–1.10), respectively.

Longitudinal HbA_{1c} Level in Association With Dementia Risk

During a median of 6 years' follow-up (ranging from 0–30 years) of the 372,287 patients with diabetes with postdiagnosis HbA_{1c} data, 23,746 (6.4%) incident dementia cases were recorded. HbA_{1c} level was significantly associated with higher risk of dementia incidence, with an HR of 1.08 (95% CI 1.07–1.09) per 1% increment of HbA_{1c} in the fully adjusted model and 1.13 or 1.14 in models 1 and 2, respectively (Table 3). In a separate analysis in which time-varying HbA_{1c} was modeled as a categorical variable with 6–7% as reference group, patients with well-controlled HbA_{1c} ($<$6%) had lower risk of dementia incidence (HR 0.86 [95% CI 0.83–0.89]), while those with HbA_{1c} levels of 8–9%, 9–10%, and $\geq$10% had 15% (95% CI 9–21), 26% (95% CI 17–34), and 40% (95% CI 32–49) increased risk of dementia incidence, respectively (Fig. 1).

Long-Term Mean and Variability of HbA_{1c} in Association With Subsequent Dementia Risk

Consistent with the results of time-varying HbA_{1c} analysis, the mean value of 3-year HbA_{1c} measurements was significantly associated with higher risk of subsequent dementia incidence after controlling for HbA_{1c} variability, with an HR of 1.04 (95% CI 1.02–1.06) per 1% increment of HbA_{1c} in model 3 and 1.05 in models 1 and 2 (Table 3). Compared with patients who had a mean HbA_{1c} level at 6–7%, those with mean HbA_{1c} levels of 8–9%, 9–10%, and $\geq$10% had 9% (95% CI 3–16), 18% (95% CI 8–28), and 30% (95% CI 17–44) increased risk of dementia incidence (model 3), respectively.

The 3-year CV of HbA_{1c}, which reflects the long-term glycemic variability, was also independently associated with higher risk of dementia incidence. After controlling for the 3-year mean HbA_{1c} level, the HRs were 1.03 (95% CI 1.01–1.04) per 1-SD increment of CV in model 3 and 1.02 in models 1 and 2 (Table 3). Compared with patients in the lowest quartile (Q1) of CV, the Q2, Q3, and Q4 groups had 6% (95% CI 1–11), 12% (95% CI 6–18), and 13%

Table 1—Baseline characteristics of participants in diabetes cohort and HbA_{1c} subcohort

Characteristics	Full diabetes cohort	HbA_{1c} subcohort	Baseline HbA_{1c} level	
			<7%	≥7%
Number of participants	457,902	372,287	216,600	155,687
Sex (male), %	52.1	53.3	51.8	55.3
Baseline age (mean), year	64.5	65.1	66.2	63.7
Ethnicity (White), %	87.5	87.5	88.6	85.9
Year of cohort entry (median)	2007	2007	2008	2005
IMD (most deprived), %	18.8	19.0	18.3	20.0
Obesity (BMI ≥30 kg/m^2), %	42.3	45.1	42.5	48.8
Current smoker, %	19.0	17.9	16.4	20.1
CHD, %	35.1	39.4	42.8	34.6
Stroke, %	6.8	7.6	8.1	6.9
Hypertension, %	85.0	92.0	92.4	91.5
CKD, %	5.9	6.6	8.3	4.2
COPD, %	3.8	4.2	4.5	3.7
Cancer, %	9.1	9.8	11.0	8.1
Duration of diabetes (mean), year	0.6	1.5	1.3	1.9
Ever use of antidiabetes drugs, %	17.1	31.1	20.0	46.5
Baseline HbA_{1c} level (mean), %	7.4	7.3	—	—
Presence of hypoglycemic events, %	0.4	0.7	0.5	1.1
Presence of microvascular complications, %	1.8	4.2	2.9	6.0

In the diabetes cohort, ethnicity, IMD, BMI, smoking status, and baseline HbA_{1c} had 69.9%, 6.7%, 11.4%, 18.5%, and 34.8% missing values, respectively. The statistics for these variables presented in this table are based on complete cases. CHD, chronic heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

(95% CI 6–19) of increased risk of dementia incidence, respectively (Fig. 1).

The subgroup analyses by sex (Supplementary Table 6) showed a stronger association between hypoglycemia and dementia risk in men (HR 1.39) than in women (HR 1.23; $P_{interaction}$ = 0.002). Results of all sensitivity analyses were similar to those of the main analyses (Supplementary Table 7).

CONCLUSIONS

This is the largest cohort study to comprehensively evaluate the association between longitudinal diabetes control and subsequent dementia risk among patients with type 2 diabetes. Our results strengthen the previous evidence on the association between hypoglycemic events and increased risk of dementia incidence among patients with diabetes. Moreover, the presence of microvascular complications, as well as high and unstable HbA_{1c} levels during follow-up, are also found to be independent risk factors for incident dementia.

Our results on hypoglycemic complications are in line with evidence from previous cohort studies. An EHR-based cohort study of 16,667 patients with type 2 diabetes showed that those with at least one severe hypoglycemic episode had higher risk of dementia than patients without such record (16). Another cohort study, using the earlier version of the U.K. CPRD (from 2003 to 2012) with 53,055 patients with type 2 diabetes, demonstrated that hypoglycemia was associated with a higher risk of subsequent dementia incidence (17). In contrast, as patients with dementia may have reduced functional ability to

Table 2—Associations between diabetic complications and risk of dementia among 457,902 patients with diabetes

Complications	Number of patients with complications	HR (95% CI) for dementia incidence		
		Model 1	Model 2	Model 3
Hypoglycemic event	19,510	1.50 (1.42–1.59)	1.44 (1.37–1.53)	1.30 (1.22–1.39)
Microvascular complications	111,248	1.22 (1.18–1.26)	1.21 (1.17–1.24)	1.10 (1.06–1.14)
Retinopathy	79,543	1.19 (1.15–1.22)	1.17 (1.14–1.21)	1.07 (1.03–1.11)
Neuropathy	44,195	1.41 (1.34–1.48)	1.36 (1.30–1.44)	1.25 (1.18–1.33)
Nephropathy	9229	1.35 (1.25–1.45)	1.31 (1.21–1.41)	1.23 (1.13–1.33)

Results are based on time-varying Cox regressions, with no-complication group as the reference group. Model 1 adjusted for age, sex, calendar year, and region; model 2 further adjusted for IMD, smoking status, BMI category, and history of comorbidities (chronic heart disease, stroke, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, and cancer); and model 3 additionally adjusted for duration of diabetes, prescriptions of antidiabetes drugs and baseline HbA_{1c} level. $P < 0.05$ in all of the analyses in this table.

Table 3—Associations between longitudinal HbA_{1c} levels of patients with diabetes and risk of dementia

HbA_{1c} measures	HR (95% CI) for dementia incidence		
	Model 1	Model 2	Model 3
Time-varying HbA_{1c} (per 1%)	1.13 (1.12–1.14)	1.14 (1.13–1.15)	1.08 (1.07–1.09)
Three-year mean HbA_{1c} (per 1%)	1.05 (1.04–1.07)	1.05 (1.04–1.07)	1.04 (1.02–1.06)
Three-year CV of HbA_{1c} (per 1 SD)	1.02 (1.00–1.04)	1.02 (1.00–1.04)	1.03 (1.01–1.04)

Results are based on time-varying Cox regressions (for time-varying HbA_{1c}) or conventional Cox regressions (for 3-year measures). Model 1 adjusted for age, sex, calendar year, and region; model 2 further adjusted for IMD, smoking status, BMI category, and history of comorbidities (chronic heart disease, stroke, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, and cancer); and model 3 additionally adjusted for duration of diabetes, prescriptions of antidiabetes drugs and diabetic complications. In addition, for the analysis of 3-year HbA_{1c} measures, the mean level and CV were mutually adjusted for in models 1 through 3, given that a moderate correlation was detected between these two variables. $P < 0.05$ in all of the analyses in this table.

achieve proper diabetes management, established dementia may in turn lead to frequent hypoglycemic episodes or other diabetic complications. A meta-analysis (18) of nine observational studies revealed a bidirectional association between hypoglycemic episode and dementia. Therefore, we have used a 2-year lag in the main analysis and 5-year lag in the sensitivity analyses to account for reverse causality bias. It has been postulated that hypoglycemia can disrupt the cerebral glucose metabolism and thus contribute to neuropathological changes (26). Previous experimental studies have shown that severe hypoglycemia could trigger apoptosis and neuronal loss (26). In this regard, hypoglycemia may not only serve as a reflection of poor management or progression of diabetes, but may also be directly implicated in the neurodegenerative process.

In terms of the relationship between microvascular diabetic complications and dementia risk, there has been one report on a predictive risk score of 10-year dementia risk for patients with type 2 diabetes (27). Among the 45 candidate predictors, the 8 strongest predictors were selected into the final prediction model, including microvascular disease (diabetic retinopathy/end-stage renal disease), diabetic foot, and acute hyper-/hypoglycemic events. Our findings further confirm the associations of overall and individual microvascular complications with risk of dementia incidence. It is likely that such complications merely represent peripheral markers of cerebral microvascular lesions (28) rather than contributing to the development of dementia through direct biological mechanisms. For instance, the retina is traditionally seen as an accessible extension of the central nervous system and may reflect possible cerebral pathology, such as cerebral small vessel disease, resulting from poor diabetes control and chronic hyperglycemia. In this context, our observed relatively weak association between retinopathy and dementia risk is intriguing. On one hand, our findings are in line with previous reports of weak direct evidence on associations between retinal microvascular changes and dementia incidence (29). For example, a report based on the Rotterdam Study found no association between retinopathy and dementia incidence (30). On the other hand, our effect estimate might have been attenuated due to underdiagnosis, as retinopathy may remain asymptomatic and undetected in the absence of routine ophthalmoscopic screening.

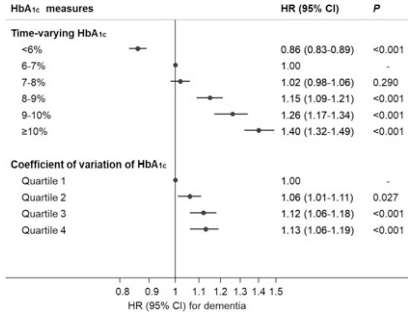

Figure 1—Associations of time-varying HbA_{1c} and 3-year CV of HbA_{1c} with the risk of dementia: results are based on fully adjusted time-varying Cox regression (for time-varying HbA_{1c}) or conventional Cox regression (for 3-year CV).

Our results of time-varying HbA_{1c} levels and long-term average HbA_{1c} levels confirm previous reports based on observational studies of much smaller sample sizes. A prospective cohort study monitored the glucose levels and dementia incidence of 2,067 older adults for a median of 6.8 years (11). Among participants with diabetes at baseline, elevated average glucose levels were associated with a higher risk of dementia. A 9-year cohort study also demonstrated that elevated longitudinal glucose level was associated with worse cognitive performance among 717 older adults with diabetes (12). A previous cohort study in participants with and without diabetes found a J-shaped association between baseline HbA_{1c} and incident dementia (31). In contrast, our results indicate a linear HbA_{1c}–dementia relationship among patients with diabetes, probably because we adjusted for hypoglycemic events or because the majority of patients in our sample had HbA_{1c} levels >5.5% (37 mmol/mol). However, another cohort study of 2,246 older adults with type 2 diabetes showed that, for those with high or moderate HbA_{1c} at baseline, a large reduction in HbA_{1c} within the 1st year of follow-up was associated with higher incidence of dementia during follow-up (13). A pioneering large randomized controlled trial (32) tested the effects of intensive glycemic control treatment strategies (target HbA_{1c} <6.0%) versus standard-care guidelines (HbA_{1c} <7.0–7.9%) on cognitive outcomes in patients with type 2 diabetes. Although the intensive glycemic therapy group had larger total brain volume at 40 months and a slower rate of gray matter loss, no significant between-group difference in the rate of clinical cognitive decline was observed (32,33). Future adequately powered randomized controlled trials on long-term glycemic control and dementia prevention in patients with diabetes are further warranted.

Our findings also suggest that glycemic variability, an acknowledged indicator for diabetes control and predictor

for mortality in older adults (15), is also independently associated with dementia risk. Currently, in the absence of an established "gold standard" measure, the CV has been recommended as a robust marker for glycemic variability (34). In accordance with our findings, a retrospective cohort study of 16,706 Chinese patients with type 2 diabetes suggested that CVs for fasting plasma glucose and HbA_{1c}, calculated during the 1st year of follow-up, were associated with increased risk of AD incidence (35). In this regard, a high and unstable glycemic level may contribute to dementia pathogenesis either through cerebrovascular lesions (28) and cerebral metabolic dysregulation (36) or as an indicator of the underlying "brain insulin resistance," shown to be associated with the AD pathological signature of brain amyloidosis, tau accumulation, and neurodegeneration (AT[N]) (10).

Studies based on EHRs are subject to potential sources of bias, which we have attempted to account for both in study design and through several sensitivity analyses. Firstly, selection bias is an acknowledged risk for studies based on real-world EHR data. In this study, this risk was mitigated by the use of a national database including data from virtually all patients registered in 8% of primary care/GP practices across the U.K. CPRD covers a wide range of urban and rural areas of diverse socioeconomic strata and has been shown to be well representative of the general population (19). Another possible limitation relates to the potential underreporting or misdiagnosis of dementia cases in EHR data sets. We maximized dementia case ascertainment by data linkage with HES and ONS databases (secondary diagnosis and cause of death). Moreover, assuming that the remaining misclassification in outcome events is independent of exposure variables, our estimates of association (i.e., HRs) are likely to have been biased toward the null rather than overestimated (37). To account for changes in dementia diagnostic criteria and the increasing diagnosis rate of dementia over time (38), we have adjusted for calendar year in all analyses and conducted a sensitivity analysis restricted to data collected after 2004, all of which produced consistent results. Future well-powered clinical studies, allowing for deep phenotyping and biomarker-based characterization of patients with dementia, are warranted to elucidate the precise contribution of diabetes-related factors in the pathogenesis of AD and other LOD forms.

EHR-based studies are also vulnerable to information bias in exposure assessments. For example, although hospital admissions or emergency department attendances following severe hypoglycemia are typically recorded in GP practices through referral letters or hospital discharge notes, some instances may be missed. Another possible limitation is that measurement of HbA_{1c} may not be regularly conducted by GPs for each patient, which may potentially affect the calculation of the CV of HbA_{1c}. To overcome such limitations, a paradigm shift in data collection methods is warranted, as lack of real-time clinical data is a shared limitation of EHR-based and prospective cohort studies. Future real-time collection of clinical data using patient-administered portable and wearable devices and real-time reporting of adverse outcomes can improve disease management and data quality for research purposes. Furthermore, the possibility of residual confounding bias cannot be ruled out. For instance, there is little information on education level and on physical/social activities in CPRD, which are known risk factors for dementia (3,39). There were 7–19% missing values for IMD, BMI, and smoking status, but little difference was observed for effect estimates in models with and without adjustment for these covariates, suggesting that the effect of residual confounding is likely small. Finally, causality cannot be established from the results of our epidemiological analyses. Further mechanistic studies are required to elucidate the precise biological mechanisms underpinning the effect of poor diabetic control on dementia risk in older adults.

This CPRD-based study has several strengths, including the large sample size (457,902 patients with diabetes and 28,627 incident dementia cases), the long follow-up period of up to 30 years, and the broad age distribution of participants. We were also able to examine multiple indicators of diabetes control (HbA_{1c} level and its variability, hypoglycemia, and microvascular complications) in relation to dementia risk and have adjusted for a large set of potential confounding factors. In addition, we have carefully accounted for reverse causality bias and conducted multiple sensitivity analyses to address issues such as data quality, change of clinical practice over time, and accuracy of dementia diagnosis, the results of which supported the robustness of our main findings.

In conclusion, this large-scale cohort study provides strong evidence that higher or unstable HbA_{1c} levels and the presence of diabetic complications in patients with type 2 diabetes are associated with higher dementia incidence. Given the lack of effective therapies for AD and other LOD forms and the long preclinical disease stage of progressively accumulating pathologies prior to clinical disease onset, the effective management of modifiable risk factors and conditions, such as type 2 diabetes (39,40), may have potential value in reducing the burden of cognitive and functional decline and dementia in the elderly population.

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