Glycaemic control, diabetic complications and risk of dementia in patients with diabetes: results from a large UK cohort study

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Abstract

Objective: Type 2 diabetes is an established risk factor for dementia. However, the roles of glycaemic 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 HbA1c levels and diabetic complications with the risk of dementia incidence among patients with type 2 diabetes.

Research Design and Methods: Data of eligible diabetes patients, aged over 50 years in the UK Clinical Practice Research Datalink from 1987 to 2018, were analysed. Time-varying Cox regressions were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for dementia risk.

Results: Among 457,902 diabetes patients, 28,627 (6.3%) incident dementia cases were observed during a median of six years follow-up. Patients with recorded hypoglycaemic events or microvascular complications were at higher risk of dementia incidence compared to those without such complications (HR [95% CI]=1.30 [1.22-1.39] and 1.10 [1.06-1.14], respectively). The HbA1c level, modelled as a time-varying exposure, was associated with increased dementia risk (HR=1.08, 95% CI: 1.07-1.09 per 1% HbA1c increment) among 372,287 diabetes patients with post-diagnosis HbA1c records. Similarly, higher coefficient of variation of HbA1c during the initial three 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 HbA1c levels and the presence of diabetic complications in patients with type 2 diabetes are associated with increased dementia risk. Effective management of glycaemia might have significant role in maintaining cognitive health among older adults with diabetes.

Introduction

The number of older adults living with Alzheimer's 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 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 nondiabetic subjects (4-6). Furthermore, several reports have linked type 2 diabetes with presence of specific AD biomarkers, such as CSF phosphorylated tau and total tau (7), reduced brain volume and fluorodeoxyglucose (FDG) 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 glycaemic control and diabetic complications in dementia development are less well understood (9,10). Reports on plasma glucose or glycosylated hemoglobin A1c (HbA1c) 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, HbA1c 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 diabetic patients, independently of HbA1c levels (15). The effect of HbA1c variability on dementia risk is less clear.

With regard to diabetic complications, extensive evidence suggests that hypoglycaemia, 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 HbA1c 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 UK Clinical Practice Research Datalink (CPRD) (19).

Research Design and Methods

Data sources

The UK CPRD GOLD database is a primary-care database that includes ongoing longitudinal collection of fully coded EHRs of over 17 million individuals, who are (or were) registered with over 700 participating general practitioner (GP) practices in the UK (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 UK (19).

Study population

Individual-level data between 1987 and 2018 were extracted for this study. Patients were included if they were aged 50 years or over at any point during their CPRD registration period and had a diagnosis of diabetes, based on relevant CPRD Medcode or a prescription of anti-diabetes drugs (oral hypoglycaemic agents or insulin) (Supplementary Table 1). In addition, eligible participants were required to have been registered in CPRD for at least one 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 the age of 30 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 two 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 two years following the first post-diabetes diagnosis HbA1c record after age 50 were excluded from the analyses of HbA1c 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 HbA1c record at age 50 or over and post diabetes diagnosis and were included in the analysis of longitudinal HbA1c levels and dementia risk.

Exposure assessment

Episode of hypoglycaemia, 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 hypoglycaemia episodes, we used codes of severe hypoglycaemia, hospital-treated hypoglycaemia, hypoglycaemia without coma and unspecified hypoglycaemia (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 HbA1c concentrations were recorded as test results and extracted using CPRD Medcode and Enttype code (Supplementary Table 3). The HbA1c value, measured as a continuous variable, was also stratified into different clinically established categories (<6%, 6-7%, 7-8%, 8-9%, 9-10%, ≥10%). For patients with at least three HbA1c records during the first three years of follow-up, mean and coefficient of variation (CV, the ratio of the standard deviation to the mean) of the three-year HbA1c measurements were estimated and assessed as additional exposure variables, reflecting the average level and variability of long-term HbA1c concentrations.

In addition, information on the following covariates was extracted: age at cohort entry, sex, calendar year of cohort entry, region in UK, index of multiple deprivation (IMD, a proxy of socio-economic status linked to CPRD), body mass index (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 anti-diabetes 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 is variably registered in CPRD and the precision of health data recording varies over time. Moreover, it is acknowledged that most cases of late onset dementia 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 database; or (3) had at least one dementia-specific drug prescription (donepezil, galantamine, rivastigmine or memantine (22)) (Supplementary Table 4). Dementia patients with diagnoses of unrelated aetiologies, such as

following HIV infection, Creutzfeldt-Jakob disease, alcoholic and drug-induced, were excluded. Among the extracted dementia cases, 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 summarised and compared between sub-cohort patients with baseline HbA1c levels <7% (53 mmol/mol) and ≥7%. Time-varying Cox proportional hazards models, with age as the underlying time-scale, were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) of dementia associated with diabetic complications or longitudinal HbA1c levels in separate analyses. Exposures were treated as time-varying variables.

In analyses of diabetic complications, the presence of hypoglycaemic episodes, 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 01/01/1987, 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 01/05/2018, 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 HbA1c level, given that glycaemic levels change over time for each diabetes patient, the time-varying Cox model was used to estimate the HR and 95% CI of dementia incidence per 1% increment (absolute value) of HbA1c among patients with at least one HbA1c record post diabetes diagnosis after age 50. In a separate Cox model, time-varying HbA1c category (<6%, 6-7%, 7-8%, 8-9%, 9-10%, ≥10%) was assessed as the exposure variable to explore the potential non-linear 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 post-diagnosis HbA1c record after age 50 (i.e., baseline HbA1c). The end of follow-up was defined as above. To account for reverse causality bias, HbA1c concentrations recorded within two years prior to dementia incidence or death were excluded.

For the analysis of long-term average level of HbA1c and its variability, the three-year mean and CV of HbA1c 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 three years after the baseline HbA1c record (to avoid concurrent bias), until the date of dementia incidence or censoring time. Patients who developed dementia or died during the first two years of follow-up were excluded. In addition, mean and CV of HbA1c were both modelled as categorical variables (<6%, 6-7%, 7-8%, 8-9%, 9-10%, ≥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 (non-smoker, current smoker, ex-smoker or missing), BMI category (<25, 25<30, ≥30 kg/m^2 or missing), and history of comorbidities; Model 3 additionally adjusted for diabetes-related factors, including duration of diabetes, presence of diabetic complications (only for HbA1c

analysis), baseline HbA1c level (only for diabetic complications analysis) and prescription of anti-diabetes drugs (no drug, only oral hypoglycaemic drug, or insulin). Covariates were also modelled as time-varying variables and updated at complication diagnosis date or each HbA1c 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, where the estimated HR reflects relative hazard of dementia conditional on patients surviving beyond 80; (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 HbA1c recorded within two years prior to dementia incidence or death in the analysis of longitudinal HbA1c; (5) excluding HbA1c records within five years prior to dementia incidence or patients who developed dementia within the first five years of follow-up to further reduce reverse causality; (6) excluding possible outlier values in HbA1c records (<4% or >12%); (7) adjusting the three-year CV of HbA1c for the possible influence of number of HbA1c records (24) (adjusted CV = CV/(total records during three-year follow-up / total records during three-year follow-up – 1)$^{1/2}$) and also stratifying the analysis by the median number of HbA1c records; (8) additionally adjusting for the average number of clinical visits per year during follow-up of each patient, since patients who visited 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). All statistical tests were two-sided, and the significance level was defined as $P<0.05$.

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 ≥30 kg/m^2) and 19.0% were self-reported current smokers; 17.1% had been prescribed anti-diabetes drugs, and the mean baseline HbA1c level was 7.4% (57 mmol/mol) (SD=2.1%). Prior to baseline, only 1986 (0.4%) patients had hypoglycaemic events and 8060 (1.8%) had microvascular complications (5928 cases with retinopathy, 2275 with neuropathy and 569 with nephropathy). During follow-up, 17,524 (3.8%) patients developed hypoglycaemic episodes and 103,188 (22.5%) patients developed microvascular complications (73,615 with retinopathy, 41,920 with neuropathy and 8660 with nephropathy).

Among the 372,287 patients included in analyses on longitudinal HbA1c, 216,600 (58.2%) had HbA1c levels at <7% (53 mmol/mol) at baseline (Table 1). Compared to patients with HbA1c <7%, those with HbA1c ≥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 anti-diabetes drug use and diabetic complications before baseline ($P<0.05$). Patients with post-diabetes diagnosis HbA1c 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 hypoglycaemic 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 1-2 (HR=1.22 and 1.21). Neuropathy and nephropathy had relatively stronger association with dementia incidence (HR [95% CI]=1.25 [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 HbA1c level in association with dementia risk

During a median of 6 years follow-up (ranging from 0-30 years) of the 372,287 diabetes patients with post-diagnosis HbA1c data, 23,746 (6.4%) incident dementia cases were recorded. HbA1c 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 HbA1c in fully adjusted model and 1.13 or 1.14 in Models 1-2 (Table 3). In a separate analysis where time-varying HbA1c was modelled as a categorical variable with 6-7% as reference group, patients with well-controlled HbA1c (<6%) had lower risk of dementia incidence (HR=0.86, 95% CI: 0.83-0.89), whilst those with HbA1c levels of 8-9%, 9-10% and ≥10% had 15% (95% CI: 9%-21%), 26% (95% CI: 17%-34%) and 40% (95% CI: 32%-49%) of increased risk of dementia

incidence, respectively (Figure 1).

Long-term mean and variability of HbA1c in association with subsequent dementia risk

Consistent with the results of time-varying HbA1c analysis, the mean value of three-year HbA1c measurements was significantly associated with higher risk of subsequent dementia incidence after controlling for HbA1c variability, with an HR of 1.04 (95% CI: 1.02-1.06) per 1% increment of HbA1c in Model 3 and 1.05 in Models 1-2 (Table 3). Compared with patients who had a stable mean HbA1c level at 6-7%, those with mean HbA1c levels of 8-9%, 9-10% and ≥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 three-year coefficient of variation (CV) of HbA1c, which reflects the long-term glycaemic variability, was also independently associated with higher risk of dementia incidence. After controlling for the three-year mean HbA1c 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 1-2 (Table 3). Compared to 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% (95% CI: 6%-19%) of increased risk of dementia incidence, respectively (Figure 1).

The subgroup analyses by sex (Supplementary Table 6) showed a stronger association between hypoglycaemia 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 hypoglycaemic events and increased risk of dementia incidence among diabetes patients. Moreover, the presence of microvascular complications, as well as high and unstable HbA1c levels during follow-up, are also found to be independent risk factors for incident dementia.

Our results on hypoglycaemic complications are in line with evidence from previous cohort studies. An EHR-based cohort study of 16,667 type 2 diabetes patients showed that those with at least one severe hypoglycaemic episode had higher risk of dementia than patients without such record (16). Another cohort study, using the earlier version of the UK CPRD (from 2003 to 2012) with 53,055 type 2 diabetes patients, demonstrated that hypoglycaemia was associated with a higher risk of subsequent dementia incidence (17). On the other hand, as dementia patients may have reduced functional ability to achieve proper diabetes management, established dementia may in turn lead to frequent hypoglycaemic episodes or other diabetic complications. A meta-analysis (18) of nine observational studies revealed a bidirectional association between hypoglycaemic episode and dementia. Therefore, we have used a two-year lag in the main analysis and five-year lag in the sensitivity analyses to account for reverse causality bias. It has been postulated that hypoglycaemia can disrupt the cerebral glucose metabolism and thus contribute to neuropathological changes (26). Previous experimental studies have shown that severe hypoglycaemia could trigger apoptosis and neuronal loss (26). In this regard, hypoglycaemia 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 type 2 diabetes patients (27). Among the 45 candidate predictors, eight strongest predictors were selected into the final prediction model, including microvascular disease (diabetic

retinopathy/end-stage renal disease), diabetic foot and acute hyper-/hypoglycaemic 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 hyperglycaemia. 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.

Our results of time-varying HbA1c levels and long-term average HbA1c 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 2067 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 HbA1c and incident dementia (31). In contrast, our results indicate a linear HbA1c-dementia relationship among diabetes patients, probably because we adjusted for hypoglycaemic

events or because the majority of patients in our sample had HbA1c levels above 5.5% (37 mmol/mol). However, another cohort study of 2246 older adults with type 2 diabetes showed that, for those with high or moderate HbA1c at baseline, a large reduction in HbA1c within the first year of follow-up was associated with higher incidence of dementia during follow-up (13). A pioneering large randomised controlled trial (RCT) (32) tested the effects of intensive glycaemic control treatment strategies (target HbA1c<6.0%) versus standard-care guidelines (HbA1c<7.0-7.9%) on cognitive outcomes in type 2 diabetes patients. Although the intensive glycaemic therapy group had larger total brain volume at 40 months and a slower rate of grey matter loss, no significant between-group difference in the rate of clinical cognitive decline was observed (32,33). Future adequately powered RCTs on long-term glycaemic control and dementia prevention in diabetes patients are further warranted.

Our findings also suggest that glycaemic 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 coefficient of variation has been recommended as a robust marker for glycaemic variability (34). In accordance with our findings, a retrospective cohort study of 16,706 Chinese patients with type 2 diabetes suggested that coefficients of variation for fasting plasma glucose (FPG) and HbA1c, calculated during the first year of follow-up, were associated with increased risk of AD incidence (35). In this regard, a high and unstable glycaemic 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 electronic health records 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 UK. CPRD covers a wide range of urban and rural areas of diverse socio-economic 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 datasets. We maximised 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 towards 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 characterisation of dementia patients, 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 (ED) attendances following severe hypoglycaemia 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 HbA1c may not be regularly conducted by GPs for each patient, which may potentially affect the calculation of the CV of HbA1c. 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 diabetes patients 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 (HbA1c level and its variability, hypoglycaemia 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 HbA1c 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 late-onset dementia forms and the long pre-clinical 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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Data Availability: This study is based on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare Products Regulatory Agency (protocol approved by the Independent Scientific Advisory Committee: No. 19_065R). According to the UK 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 Clinical Practice Research Datalink (https://www.cprd.com).

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Tables

Table 1. Baseline characteristics of participants in diabetes cohort and HbA1c sub-cohort

Characteristics	Full diabetes cohort	HbA1c sub-cohort	Baseline HbA1c 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 anti-diabetes drugs, %	17.1	31.1	20.0	46.5
Baseline HbA1c level (mean), %	7.4	7.3	-	-
Presence of hypoglycaemic events, %	0.4	0.7	0.5	1.1
Presence of microvascular complications, %	1.8	4.2	2.9	6.0

Note: IMD = index of multiple deprivation; BMI = body mass index; CHD = chronic heart disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease. In the diabetes cohort, ethnicity, IMD, BMI, smoking status and baseline HbA1c 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.

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

Complications	Number of patients with complication	HR (95% CI) for dementia incidence		
		Model 1	Model 2	Model 3
Hypoglycaemic 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)

Note: 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); Model 3 additionally adjusted for duration of diabetes, prescriptions of anti-diabetes drugs and baseline HbA1c level. $P<0.05$ in all of the analyses in this table.

Table 3. Associations between longitudinal HbA1c levels of diabetes patients and risk of dementia

HbA1c measures	HR (95% CI) for dementia incidence		
	Model 1	**Model 2**	**Model 3**
Time-varying HbA1c (per 1%)	1.13 (1.12-1.14)	1.14 (1.13-1.15)	1.08 (1.07-1.09)
Three-year mean HbA1c (per 1%)	1.05 (1.04-1.07)	1.05 (1.04-1.07)	1.04 (1.02-1.06)
Three-year coefficient of variation of HbA1c (per 1 SD)	1.02 (1.00-1.04)	1.02 (1.00-1.04)	1.03 (1.01-1.04)

Note: Results are based on time-varying Cox regressions (for time-varying HbA1c) or conventional Cox regressions (for three-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); Model 3 additionally adjusted for duration of diabetes, prescriptions of anti-diabetes drugs and diabetic complications. In addition, for the analysis of three-year HbA1c measures, the mean level and coefficient of variation were mutually adjusted for in Models 1-3, given that a moderate correlation was detected between these two variables. $P<0.05$ in all of the analyses in this table.

Figure Legend

Figure 1. Associations of time-varying HbA1c and three-year coefficient of variation of HbA1c with the risk of dementia

Results are based on fully-adjusted time-varying Cox regression (for time-varying HbA1c) or conventional Cox regression (for three-year coefficient of variation).