Research Article

Association of Hypoglycemia With Subsequent Dementia in Older Patients With Type 2 Diabetes Mellitus

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Abstract

Background: Studies have found conflicting evidence regarding the association of hypoglycemia with dementia. We evaluated an association of hypoglycemia with subsequent dementia in patients with type 2 diabetes.

Methods: This retrospective longitudinal cohort study used the Clinical Practice Research Datalink, an electronic medical records data from the United Kingdom, from 2003 to 2012. We included patients aged >65 years diagnosed with type 2 diabetes, with no prior diagnosis of dementia. Dementia was defined using diagnosis codes from medical records. All patients were followed from the date of initial diabetes diagnosis. To account for competing risk of death, we used Fine and Gray’s competing risk model to determine the association of hypoglycemia with dementia while adjusting for potential confounders. Hypoglycemia was modeled as a time-dependent covariate.

Results: Of 53,055 patients, 5.7% (n = 3,018) had at least one hypoglycemia episodes. The overall incidence rate of dementia was 12.7 per 1,000 person-years. In the fully adjusted model that controlled for all confounders, the occurrence of at least one hypoglycemia episode was associated with 27% higher odds of subsequent dementia (hazard ratio = 1.27; 95% confidence interval = 1.06–1.51). The risk increased with the number of hypoglycemia episodes: one episode (hazard ratio = 1.26; 95% confidence interval = 1.03–1.54); two or more episodes (hazard ratio = 1.50; 95% confidence interval = 1.09–2.08).

Conclusions: Hypoglycemia is associated with a higher risk of dementia and may be responsible in part for the higher risk of dementia in patients with diabetes. Alternatively, hypoglycemia may be a marker for undiagnosed cognitive impairment, and we cannot rule out the possibility of reverse causation between hypoglycemia and dementia.

Keywords: Type 2 diabetes—Dementia—Cognitive impairment—Hypoglycemia
from over 11 million patients across 674 general practices in the United Kingdom (10–12). CPRD contains information entered by general practitioners, including patients’ demographics, medical diagnoses from primary care and specialist referrals and hospital admissions, outpatient drug written prescriptions, and outpatient lab results. Clinical diagnoses recorded by general practitioners have been shown to have high validity, with a median rate of 89% of cases with a confirmed diagnosis (13). Prescription information is also well documented in the CPRD (14).

Study Population
We included patients aged >65 years and newly diagnosed with type 2 diabetes mellitus from 2003 to 2012 in the study cohort. Type 2 diabetes patients were defined based on diagnosis codes, use of antihyperglycemic drugs, or laboratory values (any glucose ≥ 200 mg/dL, fasting glucose ≥ 126 mg/dL, or hemoglobin A1c [HbA1c] ≥ 6.5%) based on American Diabetes Association diagnostic criteria (15). Patients with abnormal laboratory value were considered having diabetes if they received a prescription of antihyperglycemic agent after the abnormal lab occurrence. Patients with newly diagnosed diabetes from 2003 to 2012 were included in the study cohort. This allowed us to capture 1 year of baseline information for all patients. The first date of diabetes diagnosis or a laboratory value indicating diabetes diagnosis was defined as the index date. If both were present, the diagnosis date was given the preference. We excluded patients with dementia diagnosis in a year prior to the index date, patients with no information on baseline HbA1c, and untreated patients. Patients were allowed to enter in the cohort at any time during the study time period, that is, 2003–2012; therefore, patients can have variable follow-up time.

Outcome
The outcome variable was time to dementia. Dementia was defined by diagnosis codes from electronic medical records that have been used previously in the CPRD data (16). All patients were followed from the first date of type 2 diabetes diagnosis until they developed dementia. Patients were censored at the earliest of: if they died, dropped out of the plan, or at December 31, 2012.

Covariates
The primary independent variable, hypoglycemia, was defined based on a previously defined algorithm for the CPRD data (17). Hypoglycemia was modeled as a time-dependent variable during the study follow-up period. Diagnosis codes were used to define hypoglycemia (Supplementary Table 1). Hypoglycemia episodes are recorded by general practitioners in the CPRD data. Patients with mild or moderate hypoglycemia do not always report to their primary care physician or visit a hospital. Therefore, it is likely that prevalence of nonsevere hypoglycemia may be underestimated. However, severe hypoglycemia is recorded accurately in the CPRD data with a positive predictive value of 88.6% compared with a gold standard chart review of hospital discharge summaries (13,18).

Patient’s age, gender, baseline HbA1c, body mass index, alcohol use, smoking status, and diabetes treatment were included as covariates. Body mass index was classified as underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), and obese (>30 kg/m²) categories (19). Diabetes treatment status was identified in the follow-up time period and classified in the following categories: oral hypoglycemic agents only, insulin only, both oral hypoglycemic agents, and insulin. Based on prior literature, we identified 20 comorbidities that affect the risk of dementia (Table 1) (20,21).

Statistical Analysis
Descriptive statistics were used to describe the patient characteristics. Patient characteristics by hypoglycemia status were compared using chi-square and t tests for categorical and continuous variables, respectively. To estimate an association of hypoglycemia with dementia, we used the Fine and Gray’s competing risk model, which extends the Cox model to competing risk data by considering the subdistribution hazard. Patients may die before they develop dementia; therefore, death was the competing risk (22,23). In an unadjusted analysis, we only included hypoglycemia episodes. In a second model, we adjusted for demographic variables such as age and gender, and baseline HbA1c to reflect the severity of diabetes. In the final model, we additionally adjusted for risk factors for dementia such as alcohol use, smoking status, diabetes treatment, and the fourteen comorbidities that were associated with dementia. Comorbidities for the final competing risk model were selected using two steps. In the first step, the association of each comorbidity with dementia was assessed in a separate competing risk model, while controlling for age and gender; of 20 comorbidities, 14 were associated with dementia at the p < .20 level of significance. Fourteen comorbidities identified in step one were included in a final competing risk model. We controlled for risk factors in a hierarchical fashion to determine if the association between hypoglycemia and dementia is attenuated by adding more risk factors. Hypoglycemia episode was modeled as a time-dependent covariate in all models. To address the issues of hypoglycemia being the marker for cognitive impairment and reverse causation between hypoglycemia and dementia, we performed a sensitivity analysis by considering 1 year of lag time from the date of the first hypoglycemic episode; any patients who developed dementia, died, or were censored within a year were excluded from the analysis.

This study was approved by the Committee for the Protection of Human Subjects at Merck. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, NC). A p value of less than .05 was considered to be statistically significant.

Results
The study cohort included 53,055 patients (Figure 1). Of these patients, 5.7% (n = 3,018) had at least one hypoglycemia episode during the follow-up period; 0.8% (n = 503) had two episodes; and 0.5% (n = 314) had more than two episodes. Table 1 reports the patient characteristics by hypoglycemia status. Patients who had at least one hypoglycemia episode were more likely to be older, women, have higher HbA1c at baseline, normal weight, and greater comorbidity burden compared with patients who did not have a hypoglycemia episode. Patients were more likely to have hypoglycemia if they were prescribed insulin (Table 1).

Overall, 5.3% of patients developed dementia during the follow-up time period; 24.2% patients were censored due to the competing event of death; and 70.5% patients were censored. The incidence rate of dementia was 19.8 per 1,000 person-years among patients with hypoglycemia and 12.5 per 1,000 person-years among patients without hypoglycemia. The death rate was 33.3% among patients with hypoglycemia compared with 23.7% among patients without hypoglycemia. The median follow-up time for the cohort was 3.8 years (interquartile range = 1.8–6.3 years). Among patients who developed dementia, the median time from first hypoglycemia episode until dementia was 1.8 years (interquartile range = 0.8–3.8 years).

Table 2 shows the results for unadjusted and multivariable adjusted competing risk Cox regression models. In an unadjusted analysis, patients
who had at least one hypoglycemia episode had 48% higher odds of developing dementia compared with patients with no hypoglycemia (hazard ratio [HR] = 1.48; 95% confidence interval [CI] = 1.24–1.76). After controlling for age, gender, and baseline HbA1c, the HR for hypoglycemia attenuated to 1.35 (95% CI = 1.14–1.61). In the fully adjusted model that controlled for all confounders, at least one hypoglycemia episode was associated with 27% higher odds of dementia compared with no hypoglycemia (HR = 1.27; 95% CI = 1.06–1.51) in patients with type 2 diabetes mellitus. Patients experiencing one episode of hypoglycemia had 26% higher risk (HR = 1.26; 95% CI = 1.03–1.54), and patients experiencing two or more episodes had 50% higher risk of developing dementia (HR = 1.50; 95% CI = 1.09–2.08) compared with patients with no hypoglycemia episodes. In sensitivity analysis, the association of hypoglycemia with dementia was eliminated (HR = 0.91; 95% CI = 0.73–1.14).

Discussion

Among older adults with type 2 diabetes mellitus, hypoglycemia episodes were associated with higher risk of dementia. The risk of dementia increased with the number of hypoglycemia episodes. The risk remained statistically significant after controlling for potential confounders.

Whitmer and colleagues analyzed data from the Kaiser Permanente Northern California Diabetes Registry and found that diabetes patients with at least one hypoglycemia episode had a 44% higher risk of developing dementia (HR = 1.44; 95% CI = 1.25–1.66) (5). Another study of the National Health Insurance Research Database from Taiwan estimated that the risk of dementia was 60% higher for patients having at least one episode of hypoglycemia (HR = 1.60; 95% CI = 1.19–2.14) (4). The prospective
Elderly patients with type 2 diabetes mellitus diagnosis from 2003 to 2012 \( (N = 109,269) \)

Excluded patients with prevalent dementia \( (N = 1,962) \)

Patients with no dementia in baseline \( (N = 107,307) \)

Excluded patients with missing HbA1c in baseline \( (N = 43,268) \)

Patients with non-missing HbA1c in baseline \( (N = 64,039) \)

Excluded patients who did not receive the treatment for diabetes \( (N = 10,984) \)

Final cohort \( (N = 53,045) \)

Figure 1. Cohort derivation.

population-based Health, Aging, and Body Composition (Health ABC) study found a twofold increased risk for dementia among diabetic patients who experienced a severe hypoglycemic event compared with those who did not \( (HR = 2.09; 95\% \text{ CI} = 1.00–4.35) \) (7). The prospective Edinburgh Type 2 Diabetes Study also found severe hypoglycemia associated with both poorer initial cognitive ability and accelerated cognitive decline (24).

We found a smaller but still statistically significant risk compared with the previous studies. The difference may stem from different patient populations from different countries, different study design, and statistical methods. Lin and colleagues used claims data from Taiwan and followed diabetic patients for up to 7 years \( (\text{median follow-up} = 4.8 \text{ years}) \); potential confounders such as body mass index, alcohol, smoking, and HbA1c were not controlled for due to unavailability in claims data (4). The Health ABC study followed diabetic patients for up to 12 years \( (\text{median follow-up not given}) \) (7). Whitmer and colleagues followed diabetic patients for up to 22 years \( (\text{median follow-up} = 4.8 \text{ years}) \) and studied the effect of severe hypoglycemia on dementia (5). In our study, we followed patients for up to 9 years \( (\text{median follow-up} = 3.8 \text{ years}) \) and included all types of hypoglycemia including severe hypoglycemia that requires hospitalization as well as those reported to general practitioners. An animal model study has shown that recurrent moderate hypoglycemia episodes can, paradoxically, protect against brain damage from severe hypoglycemia (25). In contrast to previous studies, we modeled hypoglycemia as a time-dependent covariate in the Cox model and accounted for competing risk of death using Fine and Gray’s model.

A few studies found no association between hypoglycemia and dementia. The prospective Fremantle Diabetes Study in Australians found that hypoglycemia was not associated with cognitive impairment in older patients with diabetes; the study had a small sample size \( (n = 203) \) and shorter follow-up time period \( (\text{median follow-up} = 1.8 \text{ years}) \) (9). Another study, the Diabetes Control and Complications Trial followed 1,144 patients with type 1 diabetes for 18 years and did not find an association of hypoglycemia with diabetes; the study included younger patients \( (\text{mean age of} \ 27 \pm 7 \text{ years}) \), and dementia is less likely to occur in younger populations (8). Results from the Action to Control Cardiovascular Risk in Diabetes Mellitus—The Memory in Diabetes (ACCORD-MIND) and the Action in Diabetes Mellitus and Vascular Disease (ADVANCE) trials showed that patients receiving intensive glycemic control \( (\text{HbA1c < 6\%}) \) had similar cognitive outcomes compared with patients receiving standard glycemic control \( (\text{HbA1c} \text{ from} \ 7\% \text{ to} \ 7.9\%) \) (26,27). Patients in the intensive glycemic control group also had a significantly higher incidence of hypoglycemia compared with the standard control group. Neither trial assessed the direct impact of hypoglycemia episodes on cognitive impairment (28).

Animal studies and postmortem studies of individuals who suffered fatal hypoglycemia revealed that hypoglycemia leads to permanent structural and functional damage in the in cortex, frontal lobe, and hippocampus (29–31). Hypoglycemia may lead to neuronal damage due to altered glucose transport and metabolism and increase sensitivity to neurons. Stroke can be another mechanism through which hypoglycemia has a detrimental effect on the cognition. Hypoglycemia increases platelet aggregation and fibrinogen formation, and this may accelerate vascular compromise in the brain (5,32).

The relationship between hypoglycemia and dementia is complex and bidirectional, that is, hypoglycemia may increase the risk of dementia and dementia patients are more likely to experience hypoglycemic episodes (7). Underdiagnosis of dementia is common in older adults (33–35). Symptoms of cognitive decline may precede the clinical diagnosis of dementia and may be responsible for mild or moderate hypoglycemia episodes. Once cognitive decline starts, hypoglycemic episodes may become more frequent and severe and lead to a vicious cycle between hypoglycemia and dementia (36). In sensitivity analysis, where we excluded patients who developed dementia within a year of hypoglycemia, the association between hypoglycemia episodes and dementia was eliminated, which may indicate hypoglycemia episode as a marker for cognitive impairment and reverse causation between hypoglycemia and dementia. We explored using a longer lag time period \( (2 \text{ or} 3 \text{ years}) \) between hypoglycemia episode and dementia. However, that excluded most of the dementia patients, and the study did not have sufficient power for statistical analysis.

The study found several interesting factors associated with the risk of dementia. Patients with low levels of HbA1c \( (2.5–6.9) \) are more likely to develop dementia. Alcohol use and obesity were associated with a lower risk of dementia. Several systematic reviews and meta-analysis have found that light to moderate alcohol drinking, but not heavy to excessive drinking, may reduce the risk of dementia (37–39). The association of obesity and dementia is controversial. One study that followed over 2 million people over two decades reported that higher body mass index was associated with a lower risk of dementia, whereas other studies found contradictory results (40–43). Consistent with previous literature, we found that women were more likely to develop dementia compared with men (1,2).

Our study has several strengths. We used the CPRD data that are representative of UK general population in terms of age, sex, and ethnicity (12). The CPRD is an electronic medical records database that collects information for routine patient care and not for reimbursement purposes; therefore, CPRD does not suffer from traditional claims data limitations. Furthermore, the CPRD data collect information on laboratory results, including HbA1c. We used competing risk regression models to account for the competing risk of death. Our study also had limitations. We may have underestimated the true incidence of hypoglycemia. Patients who have mild or moderate hypoglycemia often do not report hypoglycemia to their primary care physician. However, severe hypoglycemia is recorded with high accuracy (13). The median follow-up time from first hypoglycemia episode until dementia was relatively short \( (<2 \text{ years}) \). It
is possible that we underestimated the dementia cases because of possible underdiagnosis and/or under-recording of dementia in the CPRD data (44). However, dementia may be recorded with more accuracy in CPRD data compared with traditional claims data. We did not distinguish between different stages/severity of dementia. Our study may suffer from protopathic bias, where the early subclinical cognitive impairment may have resulted in hypoglycemia episodes (7). It is possible that patients experiencing hypoglycemia episodes may be screened more frequently for dementia compared with patients without hypoglycemia episodes; therefore, we cannot rule out the possibility of detection bias. The effect of HbA1c during follow-up will be mediated through the hypoglycemia episode. Because we controlled for time-dependent hypoglycemia episodes, we did not control for HbA1c during the follow-up. The study spanned over 10 years; to confirm that there was no change in diagnosis or screening of dementia, we referred to National Institute for Heath and Care Excellence guidelines and did not find any evidence suggestive of any changes (45). To confirm this, we stratified the data into two time periods (2003–2007, 2008–2013) and performed the analyses. The results for the two time periods were similar to the main analysis. Given the observational nature of the study, we cannot infer causal association between hypoglycemia and dementia.

Supplementary Material

Please visit the article online at http://gerontologist.oxfordjournals.org/ to view supplementary material.

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Conflict of Interest
None.

References