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Hypoglycemic Episodes and Risk of Dementia in Older Patients with Type 2 Diabetes Mellitus

Rachel A. Whitmer¹, Andrew J. Karter¹, Kristine Yaffe², Charles P. Quesenberry Jr.¹, and Joseph V. Selby¹

¹Division of Research, Section of Etiology and Prevention, Kaiser Permanente, Oakland CA

²Departments of Psychiatry, Neurology and Epidemiology, University of California San Francisco, San Francisco, CA

Abstract

Context—Although acute hypoglycemia may be associated with cognitive impairment in children with type 1 diabetes, no studies to date have evaluated whether hypoglycemia is a risk factor for dementia in older patients with type 2 diabetes.

Objective—To determine if hypoglycemic episodes severe enough to require hospitalization are associated with an increased risk of dementia in a population of older patients with type 2 diabetes followed up for 27 years.

Design, Setting, and Patients—A longitudinal cohort study from 1980-2007 of 16,667 patients with a mean age of 65 years and type 2 diabetes who are members of an integrated health care delivery system in northern California.

Main Outcome Measure—Hypoglycemic events from 1980-2002 were collected and reviewed using hospital discharge and emergency department diagnoses. Cohort members with no prior diagnoses of dementia, mild cognitive impairment, or general memory complaints as of January 1, 2003, were followed up for a dementia diagnosis through January 15, 2007. Dementia risk was examined using Cox proportional hazard regression models, adjusted for age, sex, race/ethnicity, education, body mass index, duration of diabetes, 7-year mean glycosylated hemoglobin, diabetes treatment, duration of insulin use, hyperlipidemia, hypertension, cardiovascular disease, stroke, transient cerebral ischemia, and end-stage renal disease.

Results—At least 1 episode of hypoglycemia was diagnosed in 1465 patients (8.8%) and dementia was diagnosed in 1822 patients (11%) during follow-up; 250 patients had both dementia and at least 1 episode of hypoglycemia (16.95%). Compared with patients with no hypoglycemia, patients with single or multiple episodes had a graded increase in risk with fully adjusted hazard ratios (HRs): for 1 episode (HR, 1.26; 95% confidence interval [CI], 1.10-1.49); 2 episodes (HR, 1.80; 95% CI, 1.37-2.36); and 3 or more episodes (HR, 1.94; 95% CI, 1.42-2.64). The attributable risk of dementia between individuals with and without a history of hypoglycemia was 2.39% per year (95% CI, 1.72%-3.01%). Results were not attenuated when medical utilization rates, length

Corresponding Author: Rachel A. Whitmer, PhD Kaiser Permanente, Division of Research, Section of Etiology and Prevention 2000 Broadway Oakland, CA 94612 raw@dor.kaiser.org.

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of health plan membership, or time since initial diabetes diagnosis were added to the model. When examining emergency department admissions for hypoglycemia for association with risk of dementia (535 episodes), results were similar (compared with patients with 0 episodes) with fully adjusted HRs: for 1 episode (HR, 1.42; 95% CI, 1.12-1.78) and for 2 or more episodes (HR, 2.36; 95% CI, 1.57-3.55).

Conclusions—Among older patients with type 2 diabetes, a history of severe hypoglycemic episodes was associated with a greater risk of dementia. Whether minor hypoglycemic episodes increase risk of dementia is unknown.

Introduction

A wealth of evidence indicates that patients with diabetes mellitus are at increased risk of dementia.¹⁻⁴ However, the role of complications of diabetes as possible mechanisms in dementia has not been well studied.⁵ Hypoglycemia is a potential adverse effect of diabetes treatment, induced either by excess exogenous insulin or by excess endogenous insulin resulting from treatment with insulin secretagogues.⁶ Although some studies have reported an association between history of hypoglycemia and impaired cognitive functioning in children and young adults with type 1 diabetes,⁷⁻¹⁰ results from the Diabetes Control and Complications Trial¹¹ found no association between acute hypoglycemia and an accelerated rate of cognitive decline. To date, no research has evaluated whether or to what extent hypoglycemic episodes are a risk factor for development of dementia in populations of older patients, most of whom have type 2 diabetes.

With the increasing prevalence of type 2 diabetes worldwide, and potentially of hypoglycemia¹²⁻¹⁴ and dementia among patients with diabetes, the relationship between these conditions should be evaluated. Hypoglycemic events involve impaired nutrient delivery to the brain, may down regulate different markers of neuronal plasticity, and increase the amount of neurotoxic glutamate.^{10,15,16} While most hypoglycemia is mild and self-managed, more severe hypoglycemia can require hospitalization, may result in hypoglycemic coma, brain damage, or both, and can affect blood-brain barrier integrity.¹⁶ Despite these consequences, the possible effects of severe hypoglycemia on the risk of subsequent dementia have not been evaluated at a population level.

The objective of this study was to determine whether prior episodes of hypoglycemia that required hospitalization or emergency department (ED) visits are associated with an increased risk of dementia during 22 years of follow-up for hypoglycemia episodes and more than 4 years of follow-up for incident dementia in a large well-characterized cohort of older patients with type 2 diabetes.

METHODS

Population

We evaluated 16,667 older patients with type 2 diabetes who are members of the Kaiser Permanente Northern California Diabetes Registry. This is a well characterized diabetes population that has been the basis of a wide range of genetic,¹⁷ epidemiologic,¹⁸⁻²² and health services research²³⁻²⁵ since 1994. Kaiser Permanente of Northern California (KPNC) is an integrated, nonprofit, group practice, and prepaid health care delivery organization that provides comprehensive medical services to 3.3 million members—30% of the surrounding population. Its membership closely approximates the general population by race/ethnicity and socioeconomic status with exception for underrepresented individuals in the extreme tails of income distribution.²⁶⁻²⁸

The registry^{29,30} is an ongoing epidemiological cohort of all KPNC members with diabetes who were identified from 5 automated databases: outpatient encounter files (diagnosis of diabetes); pharmacy prescriptions for diabetes medications; glycated hemoglobin (HbA1c) values greater than 7% in laboratory files; primary hospital discharge diagnoses of diabetes; and ED records of diabetes as the reason for visit. As of January 1, 2006, the identification method was estimated to be 99% sensitive based on capture in health plan member surveys. From a medical record review conducted between 1993-1994, the registry was found to contain 2.4% false-positive diabetes diagnoses.^{31,32}

Between 1994-1997, all members of the KPNC diabetes registry were mailed a survey to collect information regarding their sociodemographics and health behaviors, with 83% responding to the survey. In a previous study, we compared the demographic composition of the diabetes survey respondents (age, sex, and socioeconomic status) with non-respondents and found no evidence suggesting respondent bias.¹⁷

Analytic Cohort

We studied individuals who were members of Kaiser Permanente at the January 1, 2003, onset date of dementia follow-up; in the KPNC diabetes registry having completed a diabetes survey; aged 55 years or older when surveyed; diagnosed with type 2 diabetes; and alive and without prior diagnoses of dementia, mild cognitive impairment (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 331.83), or general symptom memory loss (ICD-9-CM code 780.93).

Measurement of Hypoglycemia

We identified all hospitalization and ED diagnoses of hypoglycemia using codes from our hospitalization and ED database using ICD-9-CM codes 251.0 (hypoglycemic coma), 251.1 (other specified hypoglycemia), and 251.2 (hypoglycemia, unspecified). We did not include the following ICD-9-CM codes: 250.3 (diabetes mellitus with coma) because it does not distinguish between diabetic ketoacidosis or hypoglycemia; 250.8 (diabetes mellitus with other specified manifestations) because it does not specify hypoglycemia; 270.3 (leucine-induced hypoglycemia); 775.6 (neonatal hypoglycemia); and 775.0 (hypoglycemia in an infant born to a diabetic mother). We included hypoglycemic episodes from January 1, 1980, through December 31, 2002. Episodes occurring after the beginning of follow-up for dementia were excluded because of our inability to clearly discern the temporal sequence of dementia and hypoglycemia.

This method of case identification using ICD-9-CM codes has been shown to be comparable with medical records review.³³ It is a more accurate source than billing claims because there is no incentive for over coding. Evaluation of Dementia Cases Incident cases of dementia were identified from both inpatient and outpatient databases based on ICD-9-CM diagnosis codes of senile dementia uncomplicated (290.0), Alzheimer disease (331.0), vascular dementia (290.4), and dementia not otherwise specified (290.1). This ascertainment scheme has been used successfully in several recent studies of this population.³⁴⁻³⁶

Covariates

A variety of comorbid conditions that could confound the association were collected from our laboratory and inpatient discharge and outpatient databases. Diagnoses of hypertension and cardiovascular diseases (ICD-9-CM codes 395-429), and stroke (ICD-9-CM codes 431-438) were collected from inpatient and outpatient diagnostic databases (1995-2007). End-stage renal disease was identified from Kaiser Permanente's comprehensive end-stage renal disease treatment registry.

Comorbidities were combined using a simple count method and the sum was used to create a composite scale that is used in all models adjusting for comorbidities.

Patient age, education, duration of diabetes, body mass index (calculated as weight in kilograms divided by height in meters squared), and race/ethnicity were based on self-report from the survey. Race/ethnicity included 6 categories in which the patients could self identify (white, African American, Asian, Hispanic, Native American, or other). Type of diabetes was determined using an algorithm based on self reported clinical characteristics as well as inpatient and outpatient diagnoses. Diabetes treatment was evaluated using our pharmacy databases from 2002-2003 and classified as insulin only, oral agent only (i.e. insulin secretagogues such as sulfonylureas or insulin sensitizers such as metformin and thiazolidinediones), insulin and oral agent combined, or diet treatment only (i.e. neither insulin nor oral agent prescriptions). In addition to the diabetes treatment variable, we also created an insulin duration variable that consisted of the number of years of insulin use between 1994 and the end of the study. Levels of HbA1c were collected from our laboratory databases from 1995-2002 using the first and last measurements from each year to create a single, average HbA1c value during this 7-year period.

The study was approved by the institutional review board of Kaiser Permanente of Northern California and consent was waived.

Statistical Analysis

All analyses were conducted using SAS statistical software version 9.1 (SAS Institute Inc, Cary, North Carolina). Covariates by hypoglycemic status were compared using χ^2 analyses and t-tests. Age-adjusted incidence rates of dementia by hypoglycemic status were estimated using the cohort as the standard. Attributable risks (defined as absolute risk differences for dementia between patients with a history of 1 or more hypoglycemic events and those with none) and confidence intervals (CIs) were calculated. Cox proportional hazards regression models were used to examine adjusted associations of hypoglycemic episodes and dementia risk for all models. Given that dementia hazard is more a function of age than time since completion of the survey, age was chosen as the time scale in the Cox regression models. Models were adjusted for age (as a time scale), education, race/ethnicity, sex, diabetes duration, body mass index, hyperlipidemia, hypertension, cardiovascular disease, stroke, end-stage renal disease, diabetes treatment, duration of insulin use, and HbA1c level. Assuming an 8.8% prevalence of at least 1 hypoglycemic event and 1822 incident dementia diagnoses, the cohort size of 16,667 provides sufficient power of 80% to detect a hazard ratio (HR) of 1.25 or greater.

Data on hypoglycemic events were collected retrospectively and risk of initial dementia diagnosis was evaluated from January 1, 2003, forward. The analytic cohort included individuals who were alive as of January 1, 2003, with no prior diagnosis of dementia or memory impairment. "Time in" started in 2003 when the patients could be at risk for dementia; moreover, we used patient age in 2003 as the time scale, which is the most robust method to control for age effects. Follow-up time commenced with patient age at start of dementia ascertainment on January 1, 2003, to the earliest of the following events: age at incident dementia diagnosis, age at termination of health plan membership, age at death, or age at end of the study period on January 15, 2007. The association of hypoglycemic episodes with dementia risk was analyzed in 3 ways. In each method of analysis, patients having no hypoglycemic events served as the reference group and were compared with (1) those having 1 or more events; (2) those having 1, 2, or more events; and (3) those having 1, 2, 3, or more events.

To address the possibility that reverse causality could explain observed associations, we conducted 2 additional sets of analyses. In the first set, a lag of 2 years was introduced between the end of hypoglycemic ascertainment and onset of observation for risk of incident dementia, such that we only considered incident dementia cases occurring from January 1, 2005, to January 15, 2007. In the second, we introduced a longer “backward” lag of 18 years, such that we only considered the effect of hypoglycemic episodes occurring in the first 5 years of follow-up from 1980-1985, on dementia risk from 2003-2007. Each of these was intended to reduce the possibility that preclinical dementia was increasing the likelihood of hypoglycemic episodes.

Since African American race/ethnicity, stroke, and end-stage renal disease were highly correlated with the likelihood of hypoglycemia, we conducted subgroup analyses stratified by these variables to determine associations of hypoglycemic episodes with dementia risk among patients without a stroke, those without end-stage renal disease, and those not of African American race/ethnicity. We also separately analyzed the association of dementia with hypoglycemic events that were from the ED only. Finally, we performed a series of models with additional adjustments for length of health plan membership, time since first diagnosis of diabetes in the health plan, and medical utilization rate. A *P* value of less than .05 was considered to be statistically significant.

RESULTS

A total of 1822 patients (11%) had a diagnosis of dementia during a mean follow-up (starting in 2003) of 3.8 years and median of 4.8 years. The mean age of our cohort was 64.9 years at the time of the survey and 1465 patients (8.8%) had at least 1 episode of hypoglycemia from 1980-2002. Ten of the hypoglycemic episodes were hypoglycemic coma (ICD-9-CM code 251.0) and 535 episodes (36.5%) were from ED diagnoses. The number of hypoglycemic episodes increased sharply in 2000-2002, with almost 700 events during this period. Compared with patients without hypoglycemia, those with hypoglycemia were more likely to be older, African American, treated with insulin, and to have hypertension, stroke, and end-stage renal disease (Table 1). Those with at least 1 hypoglycemic event were also more likely to be diagnosed with dementia (Table 2).

Of the 1465 patients with hypoglycemia, 68.5% had 1 episode, 18% had 2 episodes, and 13.5% had 3 or more episodes. Age-adjusted incidence rates of dementia by frequency of hypoglycemic episodes were significantly elevated for patients with at least 1 episode (566.82 cases; 95% CI, 496.52-637.48 per 10 000 person-years vs. 327.6 cases; 95% CI, 311.02-343.18 per 10,000 person-years) compared with patients with no episodes (Table 2). The attributable risk of dementia for patients with 1 or more hypoglycemic episodes compared with those with no episodes was 2.39% per year (95% CI, 1.72-3.01; Table 2).

In the Cox proportional hazard models adjusted for age, body mass index, race/ethnicity, education, sex, and diabetes duration (Table 3), patients with at least 1 episode of hypoglycemia had an increased risk of dementia compared with those with no episodes (HR, 1.68; 95% CI, 1.47-1.93). Patients with 2 or more episodes appeared to be at somewhat greater risk with an HR of 2.15 (95% CI, 1.64-2.81), as did patients with 3 or more episodes (HR, 2.60; 95% CI 1.78-3.79). Further adjustment for diabetes-related comorbidities, HbA1c level, diabetes treatment, and years of insulin use (Table 3) modestly attenuated the effect, although it remained statistically significant and clinically relevant (1 episode [HR, 1.26; 95% CI, 1.10-1.49], 2 episodes [HR, 1.80; 95% CI, 1.37-2.36], and for 3 episodes [HR, 1.94; 95% CI, 1.42-2.64]).

When examining risk of dementia using the 2-year lagged model (i.e. only considering incident dementia cases that occurred between January 1, 2005, and January 15, 2007), trends were similar. In a model fully adjusted for demographics, comorbidities, HbA1c levels, diabetes treatment, and years of insulin use, patients with 1 hypoglycemic episode had an HR of 1.15 (95% CI, 0.89-1.48), 2 episodes (HR, 1.65; 95% CI, 1.10-2.48), and 3 or more episodes (HR, 2.06; 95% CI, 1.32-3.24) vs. patients with no hypoglycemic episodes.

Backward lag models that examined only hypoglycemic events that occurred from 1980 through 1985 on risk of dementia were also performed. Although there were fewer hypoglycemic events, hypoglycemia was associated with risk of dementia (1 or more episodes vs. no episodes: HR, 1.32; 95% CI, 1.02-2.13) adjusted for age, education, race/ethnicity, body mass index, comorbidities, diabetes duration, diabetes mellitus treatment, years of insulin use, and HbA1c levels.

We also performed models in which we added other variables that could be indicative of diabetes severity to the fully adjusted model (Table 3). These 3 additional models adjusted for length of health plan membership (1 episode [HR, 1.29; 95% CI, 1.10-1.53], 2 episodes [HR, 1.88; 95% CI, 1.39-2.39], and 3 episodes or more [HR, 1.76; 95% CI, 1.29-2.40] vs. no episodes), time since initial diabetes diagnosis (1 episode [HR, 1.33; 95% CI, 1.12-1.51], 2 episodes [HR, 1.94; 95% CI, 1.48-2.54], 3 episodes or more [HR, 1.70; 95% CI, 1.24-2.31] vs. no episodes), and medical utilization rate (1 episode [HR, 1.21; 95% CI, 1.10-1.45], 2 episodes [HR, 1.63; 95% CI, 1.20-2.18], and 3 episodes or more [HR, 1.63; 95% CI, 1.17-2.27] vs. those with no episodes). These models all had results similar to the main models (Table 3), although there was some mild attenuation for those with 3 episodes or more.

Stratified analyses conducted among patients without stroke, without end-stage renal disease, or not of African American race/ethnicity demonstrated similar degrees of association between hypoglycemia and dementia (Table 4). Although history of hypoglycemia was associated with end-stage renal disease, stroke, and African American race/ethnicity, the association between hypoglycemia and dementia was not limited to these factors.

Results for patients with ED events only were similar to the results for patients with any events. Compared with patients with no ED-derived hypoglycemic episodes, as determined from outpatient records, patients with 1 hypoglycemic episode resulting in an ED visit had an HR of 1.42 (95% CI, 1.12-1.78), and those with 2 or more episodes had an HR of 2.36 (95% CI, 1.57-3.55). To determine whether a hypoglycemia diagnosis from the ED may have been simply incidental, we examined the average total number of diagnoses listed for ED visits with a hypoglycemic diagnosis. The mean number was 1.6, which indicated that hypoglycemia comprised 1 of 2 diagnoses on average, and therefore was unlikely to be an incidental finding during an ED visit for an unrelated event.

COMMENT

To our knowledge, this study is the first to evaluate whether severe episodes of hypoglycemia are associated with subsequent risk of dementia in older patients with type 2 diabetes. Our results suggest that hypoglycemic episodes severe enough to require hospitalization or an ED visit are associated with increased risk of dementia, particularly for patients who have a history of multiple episodes. Specifically, we observed a 2.39% increase in absolute risk of dementia per year of follow-up for patients with history of hypoglycemia, compared with patients without a history. Although this 1-year absolute risk difference is modest, the cumulative effects would be sizeable. Moreover, our findings were independent

of glycemic control as assessed by level of HbA1c, type of diabetes treatment, and diabetes comorbidities.

There are several possible mechanisms by which hypoglycemia could increase risk of subsequent dementia in older patients. Severe hypoglycemia can result in permanent neurological sequelae including neuronal cell death, which may accelerate the process of dementia.⁶ Hypoglycemia also increases platelet aggregation and fibrinogen formation,³⁷ and this may accelerate vascular compromise in the brain. Animal studies have illustrated that hypoglycemic coma causes damage to neuronal receptors in the ca-1, subiculum dentate, and granule cell areas of the hippocampus, regions critical for learning and memory.¹⁶ Repeated episodes of hypoglycemia could affect cognition through damage to these regions, particularly in brains that may be vulnerable due to old age.

Cerebrovascular disease is also a possible mechanism for the association between episodes of hypoglycemia and increased risk of dementia. Although we carefully adjusted for acute stroke, as well as transient cerebral ischemia, it was impossible in this study to adjust for subclinical cerebrovascular events. These could only be detected with brain imaging methods and this study could not determine whether one of the mechanisms between hypoglycemia and increased dementia risk is through undiagnosed cerebrovascular damage. Given evidence regarding hypoglycemia and neurological sequelae in animal models,^{6,16,38} cerebrovascular damage is likely one of the mechanisms.

Since hypoglycemia is a consequence of excess exogenous or endogenous insulin, the association may also reflect direct effects of long-term or recurrent hyperinsulinemia. One study found that abdominal obesity, a condition associated with hyperinsulinemia, is associated with an increased risk of dementia.³⁹ Insulin could also affect the risk of dementia by direct action on neurons or changes in energy metabolism in the hippocampus and cortex when present in excess.^{40,41} Hyperinsulinemia in the periphery is associated with lower brain levels of insulin. Patients with Alzheimer disease have higher levels of insulin in the periphery and a lower level of brain produced insulin.⁴⁰⁻⁴² In animal models, insulin has also been shown to stimulate amyloid- β protein secretion and inhibit extracellular degradation of amyloid- β by competing for insulin degrading enzyme,⁴³⁻⁴⁵ suggesting a direct mechanism by which hyperinsulinemia may contribute to Alzheimer disease pathology. Hypoglycemia is also a marker for diabetes severity, and the association of hypoglycemia and dementia could be related to severity or duration of diabetes. Although we adjusted for time since initial diabetes diagnosis, comorbidities that are indicative of severity, and duration of insulin use, it is still possible that diabetes severity increases risk of dementia.

Numerous studies have evaluated whether hypoglycemia interferes with cognitive function, and some of these studies suggest that hypoglycemia affects certain cognitive domains^{8,10,46-50} while others found no effect.¹⁵ These studies have mainly been conducted in children and young adults with type 1 diabetes. Research in adults without diabetes using functional magnetic resonance imaging techniques has shown that induced hypoglycemia is associated with impaired brain function,⁵¹ and other studies in adults with type 1 diabetes suggest an association between hypoglycemia and greater cortical atrophy, altered cerebral blood, or both.⁵²

By contrast, epidemiologic findings from the Diabetes Control and Complications Trial¹¹ suggest that in young adults with type 1 diabetes, hypoglycemic episodes are not associated with higher risk of subsequent cognitive impairment during 18 years of follow-up (mean age 45 years at follow-up). The discrepancy between these findings^{11,15} and those of the

present study could be related to the young age of patients in the Diabetes Control and Complications Trial,¹¹ who therefore were less vulnerable to risks of dementia.

Older individuals are thought to have less brain reserve or brain plasticity,⁵³⁻⁵⁵ and therefore may be unable to recover from neurological insult as well as younger individuals. It is plausible that hypoglycemia could cause neurological changes that render an older patient more susceptible to dementia, but have no discernable effect on cognitive function in younger patients in whom dementia processes have not commenced. Thus, hypoglycemia may not cause large adverse effects on cognitive performance in adults younger than 60 years, but could have a greater effect on neurocognition in older individuals.⁵⁶

Our study is the first, to our knowledge, to focus on patients with type 2 diabetes; previous research has focused primarily on hypoglycemia and neurocognition in patients with type 1 diabetes. Thus far, there has been little research on predictors of neurocognition and dementia among patients with type 2 diabetes.⁵

Strengths and Weaknesses

There are several strengths of the present study. This is a large well characterized cohort of patients with type 2 diabetes that has detailed information on comorbidities, HbA1c levels, and diabetes treatment. The stability of membership in the KPNC health plan allowed us to observe the cohort for incident dementia over a prolonged period and to temporally separate hypoglycemic events from initial diagnoses of dementia. Moreover, the hypoglycemic episodes in this study were obtained from outpatient records of ED admittance or reason for hospitalization, not from self-report or billing claims. Clinicians have relatively little incentive to over-code in this setting.

A possible weakness is that our dementia diagnoses are based on clinical diagnoses obtained from electronic medical records, rather than the results of standardized neurological assessments administered periodically to all cohort members. Another potential concern is that due to the observational nature of our cohort study, we cannot be certain of the temporality of our findings, and cognitive problems due to undiagnosed dementia may have contributed to the occurrence of hypoglycemia. However, individuals with diagnoses of dementia, mild cognitive impairment, or general memory impairment before 2003 were excluded. In addition, we designed the study to increase the temporal separation of earlier hypoglycemic episodes from later occurrences of dementia and also conducted analyses with further lags between exposure to hypoglycemia and the beginning of observation for incident dementia. These lagged-model findings demonstrated similar associations. Even when considering only hypoglycemic episodes during the first 5 years of the study, when the patients were between the ages of 52 and 57 years (when dementia is highly unlikely), there was still an association with an elevated risk of dementia more than 2 decades later. Finally, our study involves the association between severe hypoglycemic episodes and risk of dementia; implications from our study do not address the role of less severe but more frequent episodes of hypoglycemia on dementia risk. The clinical significance of minor hypoglycemic episodes on dementia risk is unknown.

Implications

Currently, 2 large multicenter clinical trials of diabetes and cardiovascular disease are under way that assess the effect of intensive blood glucose control on complications in type 2 diabetes: Action to Control Cardiovascular Risk in Diabetes Mellitus (ACCORD) and Action in Diabetes Mellitus and Vascular Disease (ADVANCE). The data and safety monitoring board and the National Heart, Lung, and Blood Institute recently stopped 1 treatment group within the ACCORD trial 18 months early because patients receiving

intensive blood glucose–lowering treatment experienced increased rates of mortality.⁵⁷ The ADVANCE study, which had slightly less stringent glycemic targets, has not shown a similar effect.⁵⁸ Nevertheless, the ACCORD study findings raise safety concerns for diabetes care in older patients. Our data further suggest a need for caution in this group.

In addition to fatal end points, these 2 trials are collecting data on hypoglycemic events and cognitive function measures and in a few years will be able to add experimental evidence regarding the observations of this study. In addition, the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial, a study of adults with type 2 diabetes or prediabetes, also includes a cognitive function substudy and may yield important results regarding glycemic control and cognition. A large body of evidence suggests that individuals with diabetes are at an increased risk of dementia, yet exact mechanisms are not known^{1,2,5,40,59,60}; our study suggests a potentially modifiable mechanism. Pharmacologically induced severe hypoglycemia may be associated with neurological consequences in an older population already susceptible to dementia. More scientific studies examining hypoglycemia and cognitive performance and brain imaging sequelae in populations of older patients with type 2 diabetes are needed.

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Table 1

Population characteristics by hospital or emergency department-associated hypoglycemia

	No. (%) ^a		P Value ^b
	Hypoglycemia (n=1465)	Nonhypoglycemia (n=15,202)	
Age at survey, mean(SD), y ^c	66.32 (7.54)	64.78 (7)	<0.001
Education ^d			0.09
Elementary or grade school	108 (7.4)	1004 (6.6)	
High/trade/business school	607 (41.4)	5997 (39.3)	
College/higher degree	750 (51.2)	8222 (54.1)	
Men	804 (54.9)	8289 (54.5)	0.79
Race/ethnicity ^d			<0.001
White	877 (59.8)	9588 (63.1)	
African American	261 (17.8)	1626 (10.7)	
Hispanic	159 (10.8)	1667 (10.9)	
Asian	125 (8.5)	1917 (12.6)	
Native American	39 (2.6)	341 (2.2)	
Other	4 (0.3)	63 (0.4)	
Duration of diabetes from self-report in 1994, mean (SD), y	13.72 (9.2)	9.15 (7.9)	
Duration of Kaiser Permanente membership, mean (SD), y	22.66 (5.32)	22.98 (5.34)	0.03
Medical utilization rate 2003-2004, mean (SD), y	20.12 (16.60)	15.2 (12.71)	<0.001
Time since first diabetes diagnosis in Kaiser Permanente system, mean (SD), y	15.24 (3.59)	14.52 (2.89)	<0.001
Comorbidity ^e			
Heart disease	1224 (83.5)	9368 (61.6)	<0.001
Hyperlipidemia	1298 (88.6)	13,488 (88.7)	0.89
Hypertension	1429 (97.5)	14,557 (95.8)	0.001
Stroke	645 (43.0)	4389 (28.9)	<0.001
End-stage renal disease	167 (11.4)	416 (2.74)	<0.001
HbA _{1c} 1995-2002, mean (SD), % ^c	8.22 (1.29)	8.08 (1.30)	<0.001
Diabetes treatment type 2002-2003 ^f			<0.001
Insulin only	533 (37.75)	2157 (14.19)	
Oral only	446 (30.44)	8615 (56.67)	
Insulin and oral agents	352 (24.03)	2794 (18.38)	
Nonpharmacological-controlled	114 (7.70)	1636 (10.70)	
Years of insulin use from 1994 to censored date, mean (SD), No.	7.23 (2.6)	6.52 (2.94)	<0.001

Abbreviation: HbA_{1c}, glycated hemoglobin^aAll data are presented as No.(%) except when indicated otherwise.

^b*P* values were calculated using the χ^2 test.

^cContinuous variables.

^dDenotes N and column percents for categorical variables.

^eData collected between 1995-2007

^fBased on pharmacy data collected between January 1, 2002, and December 31, 2002

Table 2

Frequency of hypoglycemic episodes by dementia status

	No. (%)		Age-adjusted incidence rates per 10,000 person-years (95% CI)	Excess attributable risk per year, % (95% CI) ^a
	Dementia (n=1822)	Nondementia (n=14,845)		
Any hypoglycemia				
No	1572 (10.34)	13,630 (89.66)	327.60 (311.02-343.18)	
Yes	250 (16.95)	1215 (83.05) ^b	566.82 (496.52-637.48)	2.39 (1.72-3.01)
No. of hypoglycemic episodes				
0	1572 (10.34)	13,630 (89.66)	327.60 (311.02-343.18)	
1	150 (14.84)	852 (85.16)	491.73 (412.60-570.80)	1.64 (0.91-2.36)
2	57 (22.26)	201 (77.74)	761.75 (561.24-962.27)	4.34 (2.36-6.32)
3 or more	43 (20.40)	162 (79.60) ^b	755.46 (526.46-984.46)	4.28 (2.10-6.44)

Abbreviation: CI, confidence interval.

^a Attributable risk calculated as difference between rate in group and rate in reference group (0 hypoglycemic events).^b P values were less than 0.001 and were calculated using the χ^2 test.

Table 3Hypoglycemia and risk of incident dementia^a

No. of Hypoglycemic Episodes ^b	No. of Dementia Cases	Hazard Ratio (95% Confidence Interval)		
		Adjusted for Age (As Time Scale), BMI, Race/Ethnicity, Education, Sex, and Duration of Diabetes	Additionally Adjusted for Comorbidities ^c	Additionally Adjusted for 7-Year Mean HbA _{1c} Level, Diabetes Treatment, and Years of Insulin Use
1 or more	250	1.68 (1.47-1.93)	1.48 (1.29-1.70)	1.44 (1.25-1.66)
1	150	1.45 (1.23-1.72)	1.29 (1.10-1.53)	1.26 (1.10-1.49)
2	57	2.15 (1.64-2.81)	1.86 (1.42-2.43)	1.80 (1.37-2.36)
3 or more	43	2.60 (1.78-3.79)	2.10 (1.48-2.73)	1.94 (1.42-2.64)

Abbreviations: BMI, body mass index; HbA_{1c} glycated hemoglobin.^aAnalyses combined using Cox proportional hazard models.^bThe 1 or more group was compared to 0 and 1,2, and 3 or more groups were simultaneously compared to 0.^cAdjustment made using a comorbidity composite scale.

Table 4Subgroup analyses of hypoglycemia and dementia risk^a

No. of Hypoglycemic Episodes	No. With Dementia/No. in Group	Hazard Ratio (95% Confidence Interval)	
		Adjusted for Age (as Time Scale), BMI, Race/Ethnicity, Education, Sex, and Duration of Diabetes	Additionally Adjusted for 7-Year Mean HbA _{1c} Level, Diabetes Treatment, and Years of Insulin Use
Without stroke			
1	890/11,633	1.32 (1.01-1.73)	1.23 (1.02-1.76)
2		2.00 (1.31-3.04)	1.70 (1.11-2.60)
3		1.97 (1.08-3.30)	1.60 (0.96-2.71)
Without end-stage renal disease			
1	1722/16,084	1.30 (1.09-1.55)	1.30 (1.08-1.56)
2		1.70 (1.27-2.29)	1.62 (1.18-2.23)
3		2.04 (1.32-3.15)	1.93 (1.21-3.09)
Not African American			
1	1617/14,780	1.23 (1.04-1.46)	1.24 (1.03-1.48)
2		1.75 (1.34-2.29)	1.69 (1.26-2.26)
3		1.88 (1.28-2.76)	1.85 (1.23-2.80)

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin.^aAnalyses combined using Cox proportional hazard models.