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RESEARCH ARTICLE

Association of Type 1 Diabetes and Hypoglycemic and Hyperglycemic Events and Risk of Dementia

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Abstract

Objective

To determine whether severe hypoglycemic and hyperglycemic events are associated with longitudinal dementia risk in older adults with type 1 diabetes.

Methods

A longitudinal cohort study followed up 2,821 members of an integrated health care delivery system with type 1 diabetes from 1997 to 2015. Hypoglycemic and hyperglycemic events requiring emergency room or hospitalization were abstracted from medical records beginning January 1, 1996, through cohort entry. Participants were followed up for dementia diagnosis through September 30, 2015. Dementia risk was examined with Cox proportional hazard models adjusted for age (as time scale), sex, race/ethnicity, hemoglobin A1c, depression, stroke, and nephropathy.

Results

Among 2,821 older adults (mean age 56 years) with type 1 diabetes, 398 (14%) had a history of severe hypoglycemia, 335 (12%) had severe hyperglycemia, and 87 (3%) had both. Over a mean 6.9 years of follow-up, 153 individuals (5.4%) developed dementia. In fully adjusted models, individuals with hypoglycemic events had 66% greater risk of dementia than those without a hypoglycemic event (hazard ratio [HR] 1.66, 95% confidence interval [CI] 1.09, 2.53), while those with hyperglycemic events had >2 times the risk (HR 2.11, 95% CI 1.24, 3.59) than those without a hyperglycemic event. There was a 6-fold greater risk of dementia in individuals with both severe hypoglycemia and hyperglycemia vs those with neither (HR 6.20, 95% CI 3.02, 12.70).

Conclusions

For older individuals with type 1 diabetes, severe hypoglycemic and hyperglycemic events are associated with increased future risk of dementia.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CI = confidence interval; **DKA** = diabetic ketoacidosis; **HbA1c** = hemoglobin A1c; **HR** = hazard ratio; **ICD-9-CM** = International Classification of Diseases, 9th Revision, Clinical Modification; **KPNC** = Kaiser Permanente Northern California; **T1D** = type 1 diabetes; **T2D** = type 2 diabetes.

Hypoglycemia and hyperglycemia are serious complications among patients with type 1 diabetes (T1D). Severe hypoglycemia is defined as low blood sugar resulting in loss of consciousness or ability to self-manage.[1] Severe hyperglycemia results from insulin deficiency combined with metabolic acidosis and the presence of ketones (diabetic ketoacidosis [DKA]) or extremely high blood sugar and dehydration (hyperosmolar hyperglycemic state).[1] Among adults with T1D, it is estimated that the annual prevalence of severe (requiring emergency room or hospitalization) hypoglycemia is ≈12%, and the annual prevalence of severe (requiring emergency room or hospitalization) hyperglycemia is ≈5%.[2] Both forms of severe glycemic events are diabetic emergencies, and both are largely avoidable. However, when they do occur, they are potentially life-threatening and are associated with a range of immediate, dangerous health outcomes, including coma, increased hospitalization, and death.[3]

With recent advances in diabetes treatment, people with T1D are living longer than before.[4] This increased lifespan places them at risk for aging-related conditions such as dementia. Indeed, prior studies have suggested that those with T1D may be at higher risk for dementia than those without T1D, so identifying modifiable risk factors in this vulnerable patient population is a public health priority.[5,6] Glycemic control has emerged as a potentially modifiable factor associated with cognition and dementia, suggesting a future prevention target for brain health.[7-9] While studies have established an association between severe glycemic events and increased dementia risk in type 2 diabetes (T2D),[10,11] it is unknown whether this is the case in T1D. This is crucial to evaluate considering that patients with T1D are more likely to experience severe hypoglycemic events[12,13] and DKA than those with T2D.[14] In addition, these severe glycemic events have been shown to have far-reaching cerebrovascular sequelae. Severe hypoglycemia is associated with alterations in the hippocampus and cortex and neuronal loss,[15-17] while severe hyperglycemia is associated with reduced *N*-acetyl aspartate levels (an indicator of neuronal dysfunction), reduced cerebral blood flow, and cerebral edema.[18,19] It is important to evaluate whether such events in older individuals with T1D place them at higher future dementia risk. In this study, we leverage data collected over a span of 18 years to examine the associations between severe hyperglycemic and hypoglycemic events and long-term risk of dementia in a large cohort of older adults with T1D.

Methods

Study Population

The source population for this study was identified from the Kaiser Permanente Northern California (KPNC) Diabetes Registry. KPNC is an integrated health care delivery system serving a diverse population of >4 million member representative of the catchment area, with the exception of extremes of the income distribution.[20] The KPNC Diabetes Registry identifies members from 4 sources: primary hospital discharge diagnoses of diabetes, ≥2 outpatient visit diagnoses of diabetes, any prescription for a diabetes-related medication, or any record of an elevated hemoglobin A1c (HbA1c) test.

Using the KPNC Diabetes Registry from January 1, 1996, to December 31, 2013, we identified individuals who were ≥50 years of age and had T1D using the following 3 criteria, all of which had to be met: (1) at least 75% of their diagnostic codes indicate T1D, (2) filled insulin prescriptions during the study period, and (3) did not fill prescriptions of any other hypoglycemic agents.[21] Patients were considered eligible on the first day on or after January 1, 1996, that he or she was ≥50 years old and met the criteria for T1D described above. Once the patient met eligibility, exposure and covariate status were ascertained from all available data from January 1, 1996, up to 365 days after the date of eligibility. On day 366, patients entered the cohort and follow-up began. Participants were followed up for a maximum of 18 years, with end of follow-up defined as the first of the following: dementia diagnosis, death, a lapse in KPNC membership >90 days, or the end of the study period (September 30, 2015). Individuals were excluded from the cohort if they had evidence of a dementia diagnosis before cohort entry (n = 42). This study was approved by the KPNC Institutional Review Board. The requirement for patient informed consent was waived because analyses were conducted on preexisting data.

Severe Glycemic Events

Severe glycemic events were identified as episodes of hypoglycemia or hyperglycemia that resulted in inpatient or emergency department use. Events were defined as any emergency department visit with a primary diagnosis of hypoglycemia or hyperglycemia or any hospitalization with a principal diagnosis of hypoglycemia or hyperglycemia based on ICD-9-CM codes from the patient's electronic medical records between January 1, 1996, and cohort entry. The following ICD-9 codes were used to identify severe hyperglycemic episodes: secondary diabetes mellitus with hyperosmolarity (249.2), diabetes with ketoacidosis (250.1x), and diabetes with hyperosmolarity (250.2). Severe hypoglycemic events were identified with the following ICD-9 codes based on a modified algorithm: hypoglycemic coma (251.0), other specified hypoglycemia (251.1), and hypoglycemia, unspecified (251.2).[22] History of severe hypoglycemic and hyperglycemic events was treated as a binary exposure variable. Patients were also categorized according to combined

exposure to both types of glycemic events at baseline as follows: patients without any severe hypoglycemic or hyperglycemic events (no glycemic events), patients with severe hypoglycemic exposure only, patients with severe hyperglycemic exposure only, and patients with both severe hypoglycemic and severe hyperglycemic events (both glycemic events).

Dementia Diagnosis

Consistent with previous studies in this population,[8,10] dementia diagnoses were identified in electronic health records from both inpatient and outpatient visits with the following ICD-9 codes: Alzheimer disease (331.0), vascular dementia (290.4x), and other/nonspecific dementia (290.0, 290.1x, 290.2x, 290.3, 294.1, 294.2x, and 294.8).

Death

Deaths were identified through electronic medical records, California death certificates, and Social Security Administration datasets.

Covariates

Age, sex, and self-reported race/ethnicity were captured from KPNC health plan membership databases. A missing indicator was used for participants with missing data on race/ethnicity. For each participant, the HbA1c value closest to, but preceding, cohort entry was extracted from Kaiser Permanente laboratory measures. The following comorbid conditions were captured from electronic medical records between January 1, 1996, and cohort entry (using ICD-9 and Current Procedural Terminology codes) and were categorized as binary indicators (present/absent): depression (296.2, 296.3, 298.0, 300.4, 309.28, 311.x), nephropathy (250.4, 585.x, 583.81, 58.81), stroke (431.x, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.0, 434.1, 434.9, 435.0, 435.1, 435.3, 435.8, 435.9, 436.x), neuropathy (354.x, 355.x), severe retinopathy (362.02, 362.07, 362.53, 362.83, 67,228, 67,208, 67,210), peripheral artery disease (440.x, 441.x, 442.0, 442.3, 443.81, 443.9), hypertension (401.x, 402.x, 403.x, 404.x, 405.x), and hyperlipidemia (272.x).

Statistical Analysis

We examined the distribution of dementia, demographics, diabetes complications, and HbA1c by severe glycemic event status using *p* values obtained from Cox proportional hazards models with age as the time scale.[23] Age-adjusted incidence rates of dementia were estimated overall and across the following exposure categories: severe hypoglycemic event (yes/no), severe hyperglycemic event (yes/no), and combined glycemic events (neither glycemic event, hypoglycemic event only, hypoglycemic event only, or both glycemic events). Age-adjusted incidence rates of dementia were calculated from the age distribution of the US population from the 2000 US Census across the following age groups: 50 to <55, 55 to <60, 60 to <65, 65 to <70, 70 to <75, 75 to <80, 80 to <85, 85 to 90, and ≥90 years. Person-time during follow-up is allocated across the different age groups on the basis of an individual's age at the start of follow-up; as the person ages during the study, that individual's person-time is allocated across the different age groups. We also estimated cumulative incidence of dementia in 5-year increments (from 50 to ≥90) conditional on dementia-free survival until age 50 years adjusting for competing risk of death. Cox proportional hazards models with age as the time scale were implemented to estimate the association between severe hypoglycemic and hyperglycemic events and dementia. We fit models with hypoglycemic and hyperglycemic exposures modeled separately and together in the same model to examine the association of a given glycemic exposure while simultaneously adjusting for exposure to the other type of glycemic event. We also used Cox proportional hazards models to examine the risk of dementia among individuals according to their combined exposure to both types of glycemic events (no glycemic events, hypoglycemic event only, hyperglycemic event only, both glycemic events). Models were first adjusted for race/ethnicity and sex (demographics; model 1), then additionally adjusted for HbA1c (model 2), and then the following comorbid conditions that have been shown previously to be associated with dementia and severe glycemic events in populations with diabetes: depression, stroke, and nephropathy (model 3).[24-26] To explore the directionality of the association between severe glycemic events and dementia, we conducted a sensitivity analysis in which we restricted the sample to only those participants with ≥2 years of follow-up. This analytic strategy purposefully imposes a greater length of time between exposure and outcome to explore the temporality of the association between glycemic events and the development of dementia. All analyses were performed with SAS 9.4 (SAS Institute Inc, Cary, NC).

Data Availability

Data are available on reasonable request. Deidentified data from participants are available on request/approval from the corresponding author.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Institutional Review Board at KPNC.

Results

In this cohort of 2,821 older adults with T1D, over an average of 6.9 years (SD 5.0 years) of follow-up, a total of 153 patients (5.4%) received a diagnosis of dementia (table 1). The mean age at cohort entry was 56.5 years (SD 7.8 years); 48% were female; and the majority of the sample was White (81%). At cohort entry, 14.1% (n = 398) of the sample had experienced a severe hypoglycemic event, 11.9% (n = 335) had experienced a severe hyperglycemic event, and 3.1% (n = 87) had experienced both (table 1). Compared to individuals without prior severe hypoglycemic events, those with prior severe hypoglycemic events were younger and more likely to be Black. They also were more likely to have depression,

Table 1 Baseline Characteristics by Severe Hyperglycemia and Hypoglycemia Exposure Status at Baseline

		Severe hypoglycemia			Severe hyperglycemia		
	Overall (N = 2,821)	Event (n = 398)	No event (n = 2,423)	*p* Value[a]	Event (n = 335)	No event (n = 2,486)	*p* Value[a]
Age at entry, mean (SD), y	56.49 (7.80)	54.88 (7.01)	56.75 (7.90)	<0.0001	53.93 (6.06)	56.83 (7.95)	<0.0001
Female, n (%)	1,352 (47.93)	174 (43.72)	1,178 (48.62)	0.01	184 (54.93)	1,168 (46.98)	0.07
Race/ethnicity, n (%)				0.01			<0.0001
White	2,273 (80.57)	318 (79.90)	1,955 (80.69)		249 (74.33)	2,024 (81.42)	
Black	121 (4.29)	25 (6.28)	96 (3.96)		27 (8.06)	94 (3.78)	
Hispanic	148 (5.25)	24 (6.03)	124 (5.12)		24 (7.16)	124 (4.99)	
Asian	109 (3.86)	10 (2.51)	99 (4.09)		11 (3.28)	98 (3.94)	
Other	120 (4.25)	20 (5.03)	100 (4.13)		24 (7.16)	96 (3.86)	
Missing	50 (1.77)	1 (0.25)	49 (2.02)		0 (0.00)	50 (2.01)	
Complications and comorbid conditions, n (%)							
Depression	707 (25.06)	149 (37.44)	558 (23.03)	<0.0001	143 (42.69)	564 (22.69)	<0.0001
Neuropathy	518 (18.36)	104 (26.13)	414 (17.09)	0.0001	91 (27.16)	427 (17.18)	0.001
Severe retinopathy	1,204 (42.68)	225 (56.53)	979 (40.40)	0.0002	157 (46.87)	1,047 (42.12)	0.9
Nephropathy	732 (25.95)	151 (37.94)	581 (23.98)	<0.0001	147 (43.88)	585 (23.53)	<0.0001
Stroke	177 (6.27)	35 (8.79)	142 (5.86)	0.0003	32 (9.55)	145 (5.83)	<0.0001
Peripheral artery disease	303 (10.74)	59 (14.82)	244 (10.07)	<0.0001	67 (20.00)	236 (9.49)	<0.0001
Hypertension	1,598 (56.65)	266 (66.83)	1,332 (54.97)	<0.0001	231 (68.96)	1,367 (54.99)	<0.0001
Hyperlipidemia	1,476 (52.32)	240 (60.30)	1,236 (51.01)	<0.0001	212 (63.28)	1,264 (50.84)	<0.0001
HbA1c (%), mean (SD)	8.28 (1.90)	8.35 (1.99)	8.28 (1.89)	0.4	9.49 (2.47)	8.13 (1.75)	<0.0001

Abbreviation: HbA1c = glycosylated hemoglobin.
Percentages reported are column percentages.
[a] The *p* values were obtained from Cox proportional hazards models (age as time scale).

neuropathy, nephropathy, retinopathy, stroke, peripheral arterial disease, hypertension, and hyperlipidemia. Compared to participants without prior hyperglycemia, those with severe hyperglycemic events were younger, had higher HbA1c levels, and were more likely to be female and Black. They were also more likely to have neuropathy, nephropathy, stroke, peripheral arterial disease, hypertension, and hyperlipidemia (table 1). By the end of follow-up, 153 participants (5.4%) had been diagnosed with dementia, 452 (16.0%) had died, 703 (29.7%) had a lapse in health plan membership, and 1,513 (63.9%) were dementia-free and remained KPNC members.

Overall, the age-adjusted incidence rate of dementia was 14.3 per 1,000 person-years (table 2). Across all exposure categories, exposure to severe glycemic events was associated with higher incidence rates of dementia. The age-adjusted incidence rate of dementia was 26.5 per 1,000 person-years among individuals with severe hypoglycemia vs 13.2 among individuals without. The incidence rate of dementia was 79.6 per 1,000 person-years among individuals with severe hyperglycemia vs 13.4 among individuals without. For those with both severe glycemic events, the incidence rate of dementia was 98.5 per 1,000 person-years vs 12.8 among individuals without.

The cumulative incidence of dementia at any time after baseline conditional on dementia-free survival to age 50 years was consistently higher among individuals with severe hypoglycemic events compared to those without severe hypoglycemic events (figure), among those with severe hyperglycemic events compared to those without severe hyperglycemic events (figure), and among those with both hypoglycemic and hyperglycemic events compared to those with neither (figure).

Table 2 Age-Adjusted Incidence Rate of Dementia by Severe Glycemic Event Among Older Adults With Type 1 Diabetes

	Dementia, n/N (%)	Person-years	Age-adjusted incidence rate per 1,000 person-years (95% CI)
Overall	153/2,821 (5.4)	19,435.80	14.3 (11.5, 17.0)
Severe hypoglycemia			
No severe hypoglycemic event	125/2,423 (5.2)	16,889.20	13.2 (10.4, 15.9)
Severe hypoglycemic event	28/398 (7.0)	2,546.60	26.5 (9.7, 43.2)
Severe hyperglycemia			
No severe hyperglycemic event	134/2,486 (5.4)	17,530.90	13.4 (10.7, 16.1)
Severe hyperglycemic event	19/335 (5.7)	1,904.90	79.6 (−25.1, 184.2)
Combined glycemic events			
No glycemic events	116/2,175 (5.3)	15,365.96	12.77 (10.05, 15.49)
Hypoglycemic event only	18/311 (5.8)	2,164.93	23.10 (4.82, 41.38)
Hyperglycemic event only	9/248 (3.6)	1,523.26	768.10 (−708.36, 2,244.57)
Both glycemic events	10/87 (11.5)	381.65	98.54 (3.44, 193.640)

Abbreviation: CI = confidence interval.

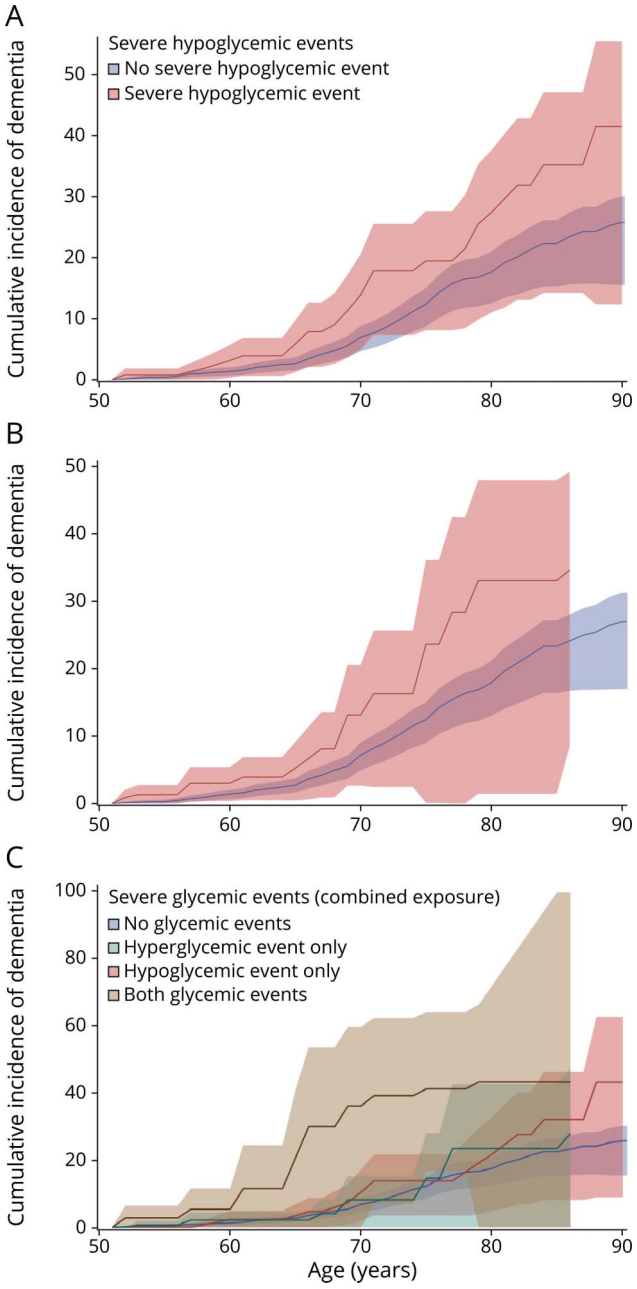
In Cox proportional hazards models, severe hypoglycemia, severe hyperglycemia, and both glycemic events were associated with increased risk of dementia. In models adjusted for age (as time scale), race/ethnicity, HbA1c, depression, nephropathy, and stroke, individuals with baseline history of severe hypoglycemia had 80% greater risk of developing dementia (hazard ratio [HR] 1.75; 95% confidence interval [CI] 1.15, 2.66; table 3). In models examining the association between severe hyperglycemic events and dementia (adjusted for the same covariates listed above), individuals with baseline history of severe hyperglycemic events had more than double the risk of developing dementia (HR 2.24; 95% CI 1.32, 3.78). Simultaneous adjustment for both glycemic events (e.g., adjusting for hypoglycemic events and hyperglycemic events in the same model) resulted in a slight attenuation of the association, although findings remained significant for both hypoglycemic and hyperglycemic events. In models adjusting for the same set of covariates above (age [as time scale], race/ethnicity, HbA1c, depression, nephropathy, and stroke), compared to those with neither glycemic event at baseline, individuals who experienced both events had a 6-fold greater risk of developing dementia during the course of follow-up (HR 6.20, 95% CI 3.02, 12.70). Among the subset of participants with a minimum of 2 years of follow-up (n = 2,326), the associations between severe hypoglycemia and dementia, severe hyperglycemia and dementia, and both glycemic events and dementia were all slightly attenuated but remained statistically significant (results not shown).

Discussion

In this study of 2,821 older adults with T1D, exposure to severe glycemic events was associated with a significantly increased risk of developing dementia. Individuals with exposure to severe hypoglycemic events were 75% more likely to develop dementia during follow-up, while those with prior exposure to severe hyperglycemic events were more than twice as likely to develop dementia. The risk of developing dementia over the course of follow-up was nearly 6 times higher in individuals with exposure to both types of severe glycemic events (hypoglycemic and hyperglycemic) vs those without exposure to either glycemic event.

In this study, we report an association between severe glycemic events and risk of dementia in T1D. Prior studies have established an association between severe glycemic events and increased dementia risk in T2D.[10,11] However, to the best of our knowledge, no prior studies have examined severe hypoglycemic or hyperglycemic events and incident dementia in a T1D population. There are a number of reasons why one could expect to see different patterns of dementia risk in T1D and T2D. Older patients with T1D are very different from older patients with T2D; because dementia diagnosis occurs in later life and T1D typically has a younger age at onset, those with T1D have lived with diabetes for much longer than those with T2D. The influence of decades-long exposure to diabetes on dementia is unknown. In addition to the longer disease duration/younger age at onset, those with T1D have had continuous insulin use since the time of diagnosis; the impact of prolonged insulin use on cognitive function/dementia has not been studied. Additionally, rates of microvascular and macrovascular complications in T1D differ as compared to T2D and the contribution of these complications to dementia risk is unknown.[27] Finally, individuals with T1D are more likely to experience severe glycemic events than those with T2D.[12-14] In this study, we evaluate the association between severe glycemic events and dementia in T1D.

Figure Cumulative Incidence of Dementia Conditional on Dementia-Free Survival Until Age 50 Years Accounting for Competing Risk of Death



(A) Severe hypoglycemic events among those with a history of a severe hypoglycemic event (red line with red shaded 95% confidence band) vs those without a history of a severe hypoglycemic event (blue line with blue shaded 95% confidence band). (B) Severe hyperglycemic events among those with history of a severe hyperglycemic event (red line with red shaded 95% confidence band) vs those without history of a severe hyperglycemic event (blue line with blue shaded 95% confidence band). (C) Combined glycemic events among those with a history of both glycemic events (brown line with brown shaded 95% confidence band), hypoglycemic event only (red line with red shaded 95% confidence band), hyperglycemic event only (green line with green shaded 95% confidence band), or no history of glycemic events (blue line with blue shaded 95% confidence band).

Pathophysiologic mechanisms by which severe glycemic events may contribute to dementia risk in T1D could result from structural changes in the brain caused by severe events or neuropathologic changes stemming from repeated exposures to dysglycemia. Prior studies, mainly in children, have shown that severe hyperglycemic events produce short-term changes in the brain (neuronal dysfunction, reduced cerebral blood flow, and cerebral edema) and are associated with altered brain growth that is observable up to 4 years after the DKA occurrence.[18,28,29] Additional studies, mainly in children and adolescents with T1D, have reported an association between a history of severe hyperglycemia and adverse cognitive effects; possible explanations include increased exposure to oxidative stress, inflammation, or insulin deficiency.[30,31] Regarding hypoglycemia in T1D, findings are more heterogeneous. Severe hypoglycemia has been associated with alterations in brain structure, including less gray matter volume; neuronal damage in several regions of the cortex, including the hippocampus; and cortical atrophy.[15-17] In children, findings generally support an association between severe hypoglycemia and decreased cognitive performance,[32-34] although not in all studies.[35,36] In young adults, however, studies examining severe hypoglycemia and cognition have generally found no association.[37,38] To the best of our knowledge, only 1 study has examined the association between severe hypoglycemia and cognitive function in older adults with T1D; in that study, severe hypoglycemia during follow-up was associated with greater cognitive decline (median follow-up 4.1 years).[39] In T2D, studies have reported an association between severe hypoglycemia and incident dementia and severe hyperglycemia and dementia.[10,11] Whether this association is true in T1D was previously unknown.

Because individuals with T1D are only recently living to older ages, optimal glycemic control in this population is not well understood. Individuals with T1D who have survived into older adulthood are a unique population. They have been living with and managing their disease for a long time and are likely to have experienced several severe glycemic events over their lifetime. As these individuals age, managing their health can become more complicated. Studies have shown that even minor changes in cognitive function can translate into significant changes in diabetes self-care; this, in turn, can lead to increased glycemic events and potentially more cognitive decline.[40] In addition, impaired awareness of hypoglycemia is a prevalent issue in this population that may contribute to increased occurrences of severe hypoglycemic events.[41] The cumulative insult of these events on the aging brain is unknown but underscores the need for improved understanding of optimal glycemic control in this growing population.

There are several strengths of the present study. To the best of our knowledge, this is the first study to investigate the long-term association of severe hypoglycemic and hyperglycemic events with incident dementia among older adults with T1D. The stability of the KPNC health plan membership allowed us to ascertain incident dementia diagnoses over a prolonged period of time and to ensure that glycemic events temporally precede diagnoses of dementia. The size of the health plan allowed us to identify a large cohort of participants with T1D

Table 3 Hazards Ratio of Severe Glycemic Events Predicting Time to Dementia Among Individuals With Type 1 Diabetes

	Model 1: Adjusted for age (as time scale), race, sex	Model 2: Model 1 + HbA1c	Model 3: Model 2 + depression, nephropathy, stroke
Severe glycemic events modeled separately			
Severe hypoglycemic event			
No severe hypoglycemic event	Ref	Ref	Ref
Severe hypoglycemic event	1.85 (1.22, 2.80)	1.94 (1.28, 2.94)	1.75 (1.15, 2.66)
Severe hyperglycemic event			
No severe hyperglycemic event	Ref	Ref	Ref
Severe hyperglycemic event	2.69 (1.63, 4.45)	2.50 (1.49, 4.19)	2.24 (1.32, 3.78)
Simultaneous modeling of both severe glycemic events			
Severe hypoglycemic event			
No severe hypoglycemic event	Ref	Ref	Ref
Severe hypoglycemic event	1.79 (1.18, 2.71)	1.84 (1.21, 2.80)	1.66 (1.09, 2.53)
Severe hyperglycemic event			
No severe hyperglycemic event	Ref	Ref	Ref
Severe hyperglycemic event	2.60 (1.57, 4.30)	2.36 (1.40, 3.97)	2.11 (1.24, 3.59)
Combined glycemic events (4-level exposure)			
No glycemic events	Ref	Ref	Ref
Hypoglycemic event only	1.34 (0.81, 2.20)	1.38 (0.84, 2.29)	1.29 (0.78, 2.14)
Hyperglycemic event only	1.59 (0.80, 3.18)	1.47 (0.73, 2.98)	1.39 (0.69, 2.83)
Both glycemic events	9.20 (4.66, 18.14)	8.41 (4.20, 16.82)	6.20 (3.02, 12.70)

Abbreviation: HbA1c = glycosylated hemoglobin.
Hazards ratios estimated for each severe glycemic event variable obtained from Cox proportional hazards models with age as time scale.

with adequate statistical power to examine the association between these potentially life-threatening events and incident dementia. We were also able to account for a number of potential comorbid conditions to examine the robustness of our findings. Furthermore, the use of KPNC allowed us to identify a cohort of patients with uniform access to medical care; this is especially important because capturing diagnoses relies on health care use. Finally, because exposure, covariate, and outcome data were obtained from patients' medical records, they are not subject to certain biases associated with self-report and recall.

This study also has some limitations. One of the main limitations of our study was the use of clinical diagnoses to identify incident cases of dementia. This may have resulted in underascertainment of the true number of incident cases given results from a recent meta-analysis suggesting high rates of undetected dementia.[42] Despite this limitation, identification of dementia cases with ICD-9 codes has been successfully used in prior studies in this population.[8,10] In addition, in a 2016 study conducted among members of KPNC using the same set of ICD-9 codes to ascertain dementia,[43] age-specific incidence rates in the KPNC sample were comparable to incidence rates reported in recent cohort studies,[44] suggesting that the use of clinical diagnoses in our integrated health care system reliably ascertains dementia cases. In a study conducted in a large integrated health care system in Washington State, using the same ICD-9 codes for dementia was reported to have high specificity (95%) and a somewhat lower sensitivity (77%) compared to prospective comprehensive case ascertainment, including cognitive testing, physical examination, informant interviews, and medical records review.[45] Another study based in the United Kingdom reported similar sensitivity (78%) and specificity (92%).[46] High specificity and lower sensitivity would result in underascertainment of dementia cases, which would bias our estimates toward the null and underestimate the association between glycemic events and dementia. A related limitation is the use of diagnosis codes from the emergency department or inpatient setting that represent the most severe events but do not address the

role of less severe but more frequent glycemic episodes on dementia risk. In addition, the observational design limits our ability to make causal inferences. That said, experimental studies on severe glycemic events are infeasible, dangerous, and unethical, and thus, our understanding of the effect of these events on brain health can be informed only by findings from observational studies. A related limitation is the inability to establish temporality between onset of dementia and occurrence of severe glycemic events; despite this limitation, findings were robust when we imposed a lag of at least 2 years between the occurrence of a severe glycemic event and the dementia diagnosis. Another limitation was the lack of information on age at diabetes onset, educational attainment, or area deprivation; this additional information would have been informative in evaluating the role of severe glycemic events on dementia risk. People who had severe glycemic events were also more likely to have a number of comorbid conditions such as depression and stroke; although we adjusted for these comorbid conditions, they could be on the causal pathway between glycemic events and dementia. We plan to explore this in future studies. Finally, because we did not have brain imaging or neuropathology data, we cannot distinguish between different subtypes of dementia and thus cannot makes inferences on whether the pathways between severe glycemic events and dementia are due to neurodegenerative changes or brain vascular injury. This will be a focus of future research.

The increasing incidence of T1D,[47,48] coupled with greater life expectancy,[4] is resulting in an unprecedented number of older adults living with and managing T1D. As this population continues to grow and age, understanding the impact that a lifetime of chronic disease and associated complications has on brain health will be crucial for informing clinical care for this population and implementing prevention strategies for those with T1D who are still early in the course of their disease. In this study of older patients with T1D, exposure to severe hypoglycemic and hyperglycemic events was independently associated with substantively increased risk of dementia; combined exposure to both hypoglycemic and hyperglycemic events was associated with an even higher risk. This study complements existing literature by extending the association between severe glycemic events and dementia to a previously unstudied population: older adults with T1D who have a much higher prevalence of these events than those with T2D. Understanding the role of glycemic control over the lifetime on brain health in older adulthood will, we hope, raise awareness regarding the importance of optimal self-care throughout the life course. Our findings suggest that exposure to severe glycemic events may have long-term consequences on brain health and should be considered as an additional motivating factor to avoid severe glycemic events throughout one's lifetime.

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Disclosure

R.A. Whitmer, P. Gilsanz, C.P. Quesenberry, A.J. Karter, and M.E. Lacy report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Name	Location	Contribution
Rachel A. Whitmer, PhD	University of California, Davis	Obtained funding; study concept and design; acquisition and interpretation of the data; drafting of the manuscript
Paola Gilsanz, ScD	Kaiser Permanente Division of Research, Oakland, CA	Study concept and design; acquisition and interpretation of the data; critical revision of the manuscript
Charles P. Quesenberry, PhD	Kaiser Permanente Division of Research, Oakland, CA	Interpretation of the data; critical revision of the manuscript
Andrew J. Karter, PhD	Kaiser Permanente Division of Research, Oakland, CA	Interpretation of the data; critical revision of the manuscript
Mary E. Lacy, PhD	University of Kentucky, Lexington	Study concept and design; analysis and interpretation of the data; drafting of the manuscript; statistical analysis

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