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ARTICLE

Traumatic brain injury associated with dementia risk among people with type 1 diabetes

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Abstract

Objective

To examine the association between traumatic brain injury (TBI) and dementia risk among a cohort of middle-aged and elderly individuals with type 1 diabetes (T1D).

Methods

We evaluated 4,049 members of an integrated health care system with T1D ≥50 years old between January 1, 1996, and September 30, 2015. Dementia and TBI diagnoses throughout the study period were abstracted from medical records. Cox proportional hazards models estimated associations between time-dependent TBI and dementia adjusting for demographics, HbA1c, nephropathy, neuropathy, stroke, peripheral artery disease, depression, and dysglycemic events. Fine and Gray regression models evaluated the association between baseline TBI and dementia risk accounting for competing risk of death.

Results

A total of 178 individuals (4.4%) experienced a TBI and 212 (5.2%) developed dementia. In fully adjusted models, TBI was associated with 3.6 times the dementia risk (hazard ratio [HR] 3.64; 95% confidence interval [CI] 2.34, 5.68). When accounting for the competing risk of death, TBI was associated with almost 3 times the risk of dementia (HR 2.91; 95% CI 1.29, 5.68).

Conclusion

This study demonstrates a marked increase in risk of dementia associated with TBI among middle-aged and elderly people with T1D. Given the complexity of self-care for individuals with T1D, and the comorbidities that predispose them to trauma and falls, future work is needed on interventions protecting brain health in this vulnerable population, which is now living to old age.

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Glossary

CDC = Centers for Disease Control and Prevention; **CI** = confidence interval; **HbA1c** = glycosylated hemoglobin; **HR** = hazard ratio; **ICD-9** = *International Classification of Diseases–9*; **KPNC** = Kaiser Permanente Northern California; **T1D** = type 1 diabetes; **TBI** = traumatic brain injury.

In 2010, over 2 million people in the United States sustained a traumatic brain injury (TBI),[1] and between 3.2 and 5.3 million Americans live with long-term disabilities due to TBI.[1,2] In addition to potential physical and functional impairment,[1] TBIs can have long-term cognitive effects, from mild cognitive dysfunction to more serious chronic diseases such as dementia.[3] Falls are the most common cause of TBIs across all age groups and contribute to 47% of TBI-related emergency department visits, hospitalizations, and deaths.[4] Older individuals with diabetes are at an elevated risk of falls,[5–7] possibly due to diabetic complications such as hypoglycemia,[8,9] peripheral neuropathy,[5] or diabetic retinopathy.[8] The link between TBIs and dementia is of particular concern for people with diabetes because dementia is associated with worse diabetes self-management and treatment[10] and increased likelihood of hypoglycemic events.[11] This may lead to a dangerous downward spiral diminishing cognitive abilities and overall health. Yet it remains unknown if TBIs among people with type 1 diabetes (T1D) is associated with dementia risk. As incidence of T1D is increasing among youth[12] and people with T1D increasingly live to an age conferring dementia risk,[13] it is important to evaluate the effect of TBI on dementia risk in elderly T1D.

Methods

Study population

Individuals enrolled within the Kaiser Permanente Northern California (KPNC) health plan were ascertained for this project if they met the definition of having a diagnosis of T1D within their electronic medical health record. Overall, KPNC provides comprehensive medical services to a diverse, multicultural population of over 4 million members within the Northern California Bay Area, Sacramento, and San Joaquin valleys. Members are representative of the greater Northern California population with some exceptions: KPNC members tend to be more educated and more affluent.[14–16]

Within the Kaiser Permanente Northern California Diabetes Registry, which is a compilation of all KPNC members with diabetes mellitus, individuals with T1D were ascertained using KPNC's electronic medical health records. The Registry, developed in 2003, identifies KPNC members with diabetes through a multiprong approach of reviewing pharmacy data, laboratory results, and diagnoses from both inpatient and outpatient records using ICD-9 codes.[17,18]

Individuals were considered to have a T1D diagnosis if they met the following 3 criteria during a review of electronic health records for all Diabetes Registry members: (1) at least 75% of their diagnostic codes indicate T1D; (2) filled an insulin prescription at any time during the study period; and (3) did not fill prescriptions of any hypoglycemic agents other than insulin.[19]

An individual's cohort entry date was the first day after January 1, 1996, that a member was at least 50 years old and diagnosed with T1D during the study period. A total of 4,049 individuals with T1D and without dementia at cohort entry were followed through September 30, 2015.

Standard protocol approvals, registrations, and patient consents

This study was approved by the KPNC internal review board. The requirement for patient informed consent was waived since analyses were conducted on preexisting data.

Traumatic brain injury

TBI was defined as ICD-9 codes from inpatient and outpatient settings for intracranial injury excluding those with skull fracture (850.x–854.x) and late effects of injuries to the nervous system (907.0) in electronic medical records. Both a history of TBI (i.e., TBI occurring between 1996 and cohort entry) as well as TBIs occurring during follow-up were included in analyses. If an individual experienced multiple TBIs, only the first TBI was included. Based off a Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report, a broader definition of TBI also included skull fractures (ICD-9 codes: 800, 801, 803, 804), injury to optic nerve and pathways (ICD-9 codes: 950.1, 950.2, 950.3), and head injuries not otherwise specified (ICD-9 code: 959.01).[4]

Dementia diagnosis

Electronic health records were utilized to identify dementia diagnoses between January 1, 1996, and September 30, 2015, from both inpatient and outpatient visits using 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). Dementia has been successfully identified using ICD-9 codes in previous studies in this population[20–26] and a similar set of ICD-9 codes had a sensitivity of 77% and a specificity of 95% compared with a consensus diagnosis of dementia utilizing medical records review, physical examination, structured interviews, and a neuropsychiatric battery.[27]

Covariates

Demographic data, including age, sex, and self-reported race and ethnicity, were extracted from KPNC health plan

membership databases. Baseline glycosylated hemoglobin (HbA1c) was obtained from the Kaiser Permanente laboratory measurement most proximal to baseline. The following baseline diabetes complications were ascertained from the KPNC electronic health record between January 1, 1996, and cohort entry using ICD-9 code definitions: nephropathy (ICD-9 codes: 250.4x, 585x, 583.81x, 581.81x), neuropathy (ICD-9 codes: 354.x, 355.x), stroke (ICD-9 codes: 431.x, 430.x, 433.x1, 434.x, 435.x excluding 435.2x), peripheral artery disease (ICD-9 codes: 440.x, 441.x, 442.0, 442.3, 443.81, 443.9), depression (ICD-9 codes: 296.2x, 296.3x, 298.0x, 300.4x, 309.0x, 309.28, 311), and severe hypoglycemic (ICD-9 codes: 251.0, 251.1, 251.2) or hyperglycemic (ICD-9 codes: 250.1x, 250.2x, 249.2x) events. Missing indicators were used for those missing data on HbA1c (n = 307) or race (n = 113); there were no other missing data.

Statistical analysis

We examined the distribution of characteristics of members with and without TBI using χ^2 and *t* tests.

Cox proportional hazards models with age as the time scale estimated the association between narrow and broader definitions of TBI and dementia risk. Covariates were added in 5 groups: demographics (age, race, sex), microvascular complications (neuropathy, nephropathy), macrovascular disease (stroke, peripheral artery disease), mental health (depression), and glycemic control (HbA1c, dysglycemic events). Possible effect modification by sex, stroke, or severe dysglycemic events was examined through interactions terms. Members were followed until dementia diagnosis, death, lapse in KPNC membership, or the end of the study period (September 30, 2015). Deaths were ascertained from KPNC hospital records, California death certificates, and Social Security Administration datasets.

To diminish the likelihood of reverse causation, we examined the risk of dementia diagnosis occurring more than 1 year after TBI diagnosis compared to individuals with no TBI diagnosis. Covariates were added to the Cox proportional hazards models (age as time scale) in the manner described above.

We conducted 2 analyses examining the association between a history of TBI at cohort entry and dementia accounting for the competing risk of death. First, the Fine and Gray regression model was implemented to estimate the HR of dementia accounting for the competing risk of death.[28] Second, we estimated the 5- to 30-year cumulative incidence of dementia in 5-year increments conditional on survival free of dementia until age 50. These estimates were obtained using the Practical Incidence Estimator macro, which incorporates information on age-specific death rates.[29]

All statistical analyses were conducted on SAS statistical software version 9.3 (SAS Institute, Cary, NC). A *p* value below 0.05 was considered statistically significant.

Data availability

Data are available to qualified investigators from the Kaiser Permanente Institutional Review Board Institutional Data Access/Ethics Committee for the purposes of replicating procedures and results.

Results

Overall, the mean age at entry was 57.0 years (SD 9.2 years), 53% of participants were male, and 22% were nonwhite (table 1). Four percent of the sample (n = 178) experienced a TBI, 9% (n = 348) experienced a TBI/head injury, and 5% (n = 212) developed dementia. Participants were followed for an average of 5.8 years (SD 5.3 years). Among the 23 individuals who developed dementia after a TBI, there was an average of 4.1 years between TBI and dementia date (SD 4.4; range 0.003–15.8 years). The time from TBI to dementia diagnosis was within 1 year for 8 individuals (34.8%), between 1 and 3 years for 5 individuals (21.7%), between 4 and 8 years for 6 individuals (26.1%), and between 8 and 16 years for 4 individuals (17.4%). Compared to those without TBI, those with TBI were more likely to have baseline neuropathy, stroke, and depression. By the end of follow-up, 21% of the sample had died, 25% had a lapse in health plan membership greater than 90 days, and 49% survived dementia-free and remained members.

Adjusting for demographics, people with TBI had 3.8 times the risk of developing dementia than individuals without TBI (hazard ratio [HR] 3.77; 95% confidence interval [CI] 2.43, 5.85; table 2). This association remained strong after adjusting for demographics, microvascular and macrovascular complications, depression, HbA1c, and severe dysglycemic events (HR 3.64; 95% CI 2.34, 5.68). There was no evidence of effect modification by sex (TBI * sex interaction term *p* value = 0.58), baseline stroke (TBI * stroke interaction term *p* value = 0.90), or severe hypoglycemia (TBI * hypoglycemia interaction term *p* value = 0.50). There was evidence of the effect of TBI being worse among people with severe hyperglycemia (TBI * hyperglycemia interaction term *p* value = 0.003; $HR_{TBI,\ hyperglycemia}$ 4.38, 95% CI 1.18, 16.24; $HR_{TBI,\ no\ hyperglycemia}$ 3.57, 95% CI 2.23, 5.71); however, these results should be interpreted with caution due to small numbers.

TBI continued to be associated with dementia when excluding dementia cases occurring within 1 year of TBI diagnosis. Individuals who experienced a TBI had more than double the risk of dementia more than 1 year after TBI diagnosis compared to individuals without TBI (table 3).

The broader definition of TBI was also associated with dementia risk in models adjusting for demographics (HR 2.91; 95% CI 2.01, 4.20; table 4) and in fully adjusted models (HR 3.03; 95% CI 2.09, 4.39). There was no evidence that the relationship between the broader definition of TBI and dementia was modified by sex (TBI * sex interaction term *p* value = 0.29), baseline stroke (TBI * stroke interaction term *p*

Table 1 Baseline characteristics by traumatic brain injury (TBI) during study period

	Overall, n (%) or mean (SD)	No TBI, n (%) or mean (SD)	TBI, n (%) or mean (SD)	*p* Value
Total	4,049 (100)	3,871 (95.6)	178 (4.4)	
Dementia	212 (5.2)	189 (4.9)	23 (12.9)	<0.001
Age, y, mean (SD)				
At entry	57.0 (9.2)	57.0 (9.3)	55.8 (7.9)	0.06
At dementia diagnosis	63.4 (9.0)	72.4 (9.5)	65.9 (10.3)	<0.01
Sex				0.75
Female	1913 (47.3)	1831 (47.3)	82 (46.1)	
Male	2,136 (52.8)	2040 (52.7)	96 (53.9)	
Race and ethnicity				0.06
White	3,142 (77.6)	3,006 (77.7)	136 (76.4)	
Black	220 (5.4)	208 (5.0)	12 (6.7)	
Hispanic	247 (6.1)	237 (5.6)	10 (5.6)	
Asian	160 (4.0)	153 (3.8)	7 (3.9)	
Other	167 (4.1)	154 (3.9)	13 (7.3)	
Missing	113 (2.8)	113 (2.7)	0 (0)	
Comorbidities and complications				
Nephropathy	661 (16.3)	628 (16.2)	33 (18.5)	0.41
Neuropathy	530 (13.1)	489 (12.6)	41 (23.0)	<0.001
Stroke	170 (4.2)	152 (3.9)	18 (10.1)	<0.001
Peripheral artery disease	286 (7.0)	269 (7.0)	17 (9.6)	0.19
Depression	696 (17.2)	649 (16.8)	47 (26.4)	<0.01
Hypoglycemic event	487 (12.3)	459 (11.9)	28 (15.7)	0.12
Hyperglycemic event	267 (6.6)	254 (6.6)	13 (7.3)	0.70
HbA1c, mean (SD)	8.0 (1.7)	8.0 (1.7)	8.1 (1.9)	0.88

Abbreviation: HbA1c = glycosylated hemoglobin.
Percentages are shown as column percentages. *p* Values obtained from χ^2 tests (for binary or categorical variables) and *t* tests (for continuous variables).

value = 0.43), severe hypoglycemia (TBI * hypoglycemia interaction term *p* value = 0.73), or severe hyperglycemia (TBI * hyperglycemia interaction term *p* value = 0.31).

In Fine and Gray regression models adjusted for demographics and accounting for the competing risk of death, a history of TBI at cohort entry (narrow definition; n = 59) was associated with more than triple the risk of dementia (HR 3.50; 95% CI 1.58, 6.65; table 5). The association persisted after further controlling for microvascular and macrovascular complications, depression, HbA1c, and dysglycemic events and TBI continued to be associated with almost a 3-fold increase in dementia risk (HR 2.91; 95% CI 1.29, 5.68).

The estimates of cumulative incidence of dementia, which account for death rates, were consistently higher for individuals with a history of TBI at cohort entry. However, the CIs were very wide due to the small number of dementia cases and encompass the CIs of those without a history of TBI at cohort entry (table 6, figure). The 15-year cumulative incidence for people with TBI was 22.38% (95% CI 0.29%, 41.15%) compared to 2.90% (95% CI 1.85%, 3.79%) among people without TBI.

Discussion

In a large cohort of people with T1D at least 50 years old, individuals who experienced TBI had 3.6 times the risk of developing dementia compared to individuals without TBI even after adjusting for demographics, depression, microvascular and macrovascular complications, HbA1c, and severe

Table 2 Traumatic brain injury and risk of dementia in individuals with type 1 diabetes

Adjusted for	HR (95% CI)
Demographics	3.77 (2.43, 5.85)
Demographics and microvascular complications	3.68 (2.37, 5.70)
Demographics and macrovascular complications	3.43 (2.20, 5.34)
Demographics and depression	3.67 (2.37, 5.68)
Demographics and HbA1c	3.95 (2.54, 6.13)
Demographics and dysglycemic events	3.80 (2.45, 5.89)
Demographics, microvascular and macrovascular complications, depression, HbA1c, and dysglycemic events	3.64 (2.34, 5.68)

Abbreviations: CI = confidence interval; HbA1c = glycosylated hemoglobin; HR = hazard ratio.
HRs estimated from Cox proportional hazards models with age as time scale. Demographics include age, sex, and race/ethnicity. Microvascular complications include neuropathy and nephropathy. Macrovascular complications include stroke and peripheral artery disease.

Table 4 Hazard ratio (HR) of broader definition of traumatic brain injury and risk of dementia among individuals with type 1 diabetes

Adjusted for	HR (95% CI)
Demographics	2.91 (2.01, 4.20)
Demographics and microvascular complications	2.83 (1.95, 4.09)
Demographics and macrovascular complications	2.79 (1.93, 4.04)
Demographics and depression	2.82 (1.95, 4.08)
Demographics and HbA1c	3.19 (2.21, 4.61)
Demographics and dysglycemic events	2.91 (2.02, 4.21)
Demographics, micro- and macrovascular complications, depression, HbA1c, and dysglycemic events	3.03 (2.09, 4.39)

Abbreviations: CI = confidence interval; HbA1c = glycosylated hemoglobin; HR = hazard ratio.
HRs estimated from Cox proportional hazards models with age as time scale. Microvascular complications include neuropathy and nephropathy. Macrovascular complications include stroke and peripheral artery disease.

dysglycemic events. A broader definition of TBI based off work by the CDC was associated with approximately a threefold risk of dementia. In models accounting for the competing risk of death, a history of TBI at cohort entry was associated with almost a threefold dementia risk adjusting for demographics, depression, microvascular and macrovascular complications, HbA1c, and severe dysglycemic events. The 15-year cumulative incidence of dementia among individuals with TBI history at cohort entry was almost 8 times that of people without TBI (2.9% compared to 22.4%). However, the CIs overlap likely due to small numbers and the difference in cumulative incidence rates should be interpreted with caution. Given the large social and economic burden of dementia, coupled with the lack of disease-modifying treatments, it is critical that the link between TBI and dementia among people with T1D be further explored.

Our results suggest that the harmful effect of TBI on dementia risk may be greater among individuals with T1D than the general population. Studies examining the association between TBIs and dementia among the general population have had mixed results.[3,30–32] A recent meta-analysis including 32 studies found that head injuries in the general population were associated with a 63% increased risk of dementia and a 51%

Table 3 Risk of dementia at least 1 year after traumatic brain injury diagnosis among individuals with type 1 diabetes

Adjusted for	HR (95% CI)
Demographics	2.45 (1.44, 4.17)
Demographics and microvascular complications	2.39 (1.40, 4.06)
Demographics and macrovascular complications	2.24 (1.31, 3.82)
Demographics and depression	2.38 (1.40, 4.04)
Demographics and HbA1c	2.55 (1.50, 4.33)
Demographics and dysglycemic events	2.46 (1.50, 4.33)
Demographics, microvascular and macrovascular complications, depression, HbA1c, and dysglycemic events	2.35 (1.38, 4.02)

Abbreviations: CI = confidence interval; HbA1c = glycosylated hemoglobin; HR = hazard ratio.

Table 5 Risk of dementia associated with baseline traumatic brain injury accounting for competing risk of death among individuals with type 1 diabetes

Adjusted for	HR (95% CI)
Demographics	3.50 (1.58, 6.65)
Demographics and microvascular complications	3.39 (1.53, 6.46)
Demographics and macrovascular complications	2.90 (1.29, 5.62)
Demographics and depression	3.32 (1.49, 6.37)
Demographics and HbA1c	3.59 (1.62, 6.83)
Demographics and dysglycemic events	3.50 (1.58, 6.65)
Demographics, microvascular and macrovascular complications, depression, HbA1c, and dysglycemic events	2.91 (1.29, 5.68)

Abbreviations: CI = confidence interval; HbA1c = glycosylated hemoglobin; HR = hazard ratio.
HRs estimated from Fine and Gray regression models with time since cohort entry as time scale. Demographics include age at cohort entry, sex, and race/ethnicity. Microvascular complications include neuropathy and nephropathy. Macrovascular complications include stroke and peripheral artery disease.

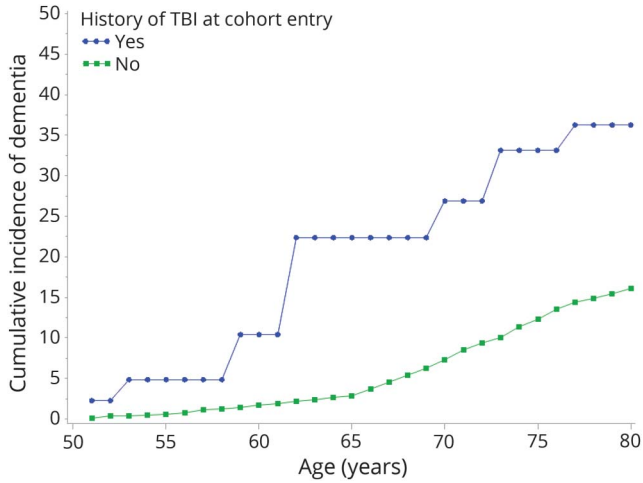
Table 6 Cumulative incidence of dementia by history of traumatic brain injury (TBI) at cohort entry conditional on dementia-free survival until age 50

	No history of TBI cumulative incidence (95% CI)	History of TBI cumulative incidence (95% CI)
5 years risk	0.60 (0.22, 0.96)	4.87 (0.00, 11.54)
10 years risk	1.71 (0.99, 2.36)	10.40 (0.00, 22.72)
15 years risk	2.90 (1.85, 3.79)	22.38 (0.29, 41.15)
20 years risk	7.26 (5.14, 8.81)	26.87 (0.00, 46.72)
25 years risk	12.29 (8.95, 14.36)	33.12 (0.00, 55.46)
30 years risk	16.14 (11.59, 18.49)	36.34 (5.40, 59.29)

Abbreviation: CI = confidence interval.

increased risk of Alzheimer disease.[32] In a study including more than 3 million individuals, a mild case of TBI was associated with 63% greater risk of dementia compared to individuals without TBI, while those with severe TBI had double the dementia risk, and those with multiple TBI had 2.8 times the risk of dementia.[33] Consistent with some,[33] but not all prior studies,[31] we found a strong association between TBI and dementia even after excluding dementia cases occurring within the first year after TBI diagnosis when possible bias due to reverse causation is greatest. However, it is challenging to compare our results with other studies given possible differences in age, TBI severity, and time since TBI. Future studies including both people with and without T1D in their sample will be better positioned to directly compare the magnitude of the effect of TBI on dementia risk across the 2 groups.

Figure Cumulative incidence of dementia by baseline traumatic brain injury (TBI) status conditional on dementia-free survival until age 50



TBIs trigger many neurotoxic events, ranging in timing from acute (e.g., axonal shearing, vasospasm ischemia) to secondary (e.g., inflammation, oxidative stress, apoptosis) to chronic (e.g., increased levels of amyloid precursor protein, hyperphophorylation of tau).[34] It has been hypothesized that several of these events could elevate risk of dementia including inflammation, oxidative stress, and the production of β-amyloid.[35] TBIs also trigger perturbations in brain glucose metabolism resulting in an increased demand for glucose, especially in the first 48 hours.[36,37] It has been estimated that in the general population, roughly 40% of patients with TBI experience hyperglycemia, a risk factor for oxidative stress.[37]

Cognitive reserve (i.e., resilience to neuropathology) may be a key role in mitigating the effects of TBI on dementia risk. It has been hypothesized that TBIs occurring at older ages may be more strongly associated with dementia risk than those occurring at younger ages due to declines in cognitive reserves associated with aging.[35] Similarly, individuals with T1D may already have greater levels of cerebrovascular damage (i.e., less cognitive reserve), leaving them more susceptible to the harmful effects of TBIs. For example, repeated exposure to hyperglycemia has been associated with gray matter density loss.[38,39] Animal models suggest that those with diabetes experienced greater levels of chronic oxidative stress that worsened their neurologic dysfunction after brain injury than those without diabetes.[40]

The primary strength of this study is the uniquely large cohort of over 4,000 people with T1D ages 50 and above with information on a wide range of microvascular and macrovascular complications as well as baseline HbA1c. Another strength is the high level of membership stability, which enabled us to follow this cohort up to 19 years. However, our study is not exempt from limitations. We only have information on diabetes beginning in 1996 and therefore are unable to examine if longer duration of T1D is associated with a greater risk of TBI. Another limitation of the study is that dementia diagnoses were not confirmed via medical record review. However, a previous study utilizing a similar set of diagnostic codes showed 77% sensitivity and 95% specificity compared with a consensus diagnosis of dementia utilizing medical records review, structured interviews, clinical evaluation, and various cognitive tests.[27] Due to small numbers, we are unable to explore if the association between TBI and dementia varies by time since TBI or type of brain injury. We cannot rule out the possibility of reverse causation as the mean number of years between TBI and dementia diagnosis was 4.1 years. We are unable to examine the direct effect of TBI on brain health due to a lack of brain imaging. We also do not have information regarding the cause or severity of the TBI. Additional studies in other large-scale diabetes databases should be conducted to see if these findings are replicated and assess for possible effect modification by diabetes duration, time since TBI, or brain injury type.

This study demonstrates dramatic increases in risk of dementia among people with T1D who experience a TBI independent of

micro complications and macro complications, depression, severe dysglycemic events, and HbA1c levels. Hypoglycemia and proprioception dysfunction associated with peripheral neuropathy put patients with T1D at uniquely elevated risk of TBI, and thus ultimately increase the likelihood of dementia. Dementia, in turn, worsens diabetes self-management and treatment[10] and may result in increased likelihood of hypoglycemic events[41] and neuropathic damage. This could trigger a dangerous downward spiral diminishing cognitive abilities, overall health, and safety. Relatedly, individuals with comorbid dementia and diabetes have reduced levels of activities of daily living and substantial reliance on assistance for personal care.[42] Given the limited treatment options once a TBI has occurred and the strong relationship between TBI and dementia, it is important for future research to identify modifiable risk factors for TBI and explore possible interventions aimed at reducing the risk of TBI among people with T1D and the general population. Lower levels of cognitive reserve may place individuals with T1D at greater risk of the deleterious effects of TBI, which may explain the greater magnitude of dementia associated with TBI in this sample than in prior studies. Given the complexity of self-care for elderly individuals with T1D, and the comorbidities that predispose them to trauma and falls, future work is needed on preventive measures for protecting brain health in this vulnerable population, which is now living to old age.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Author contributions

R.A. Whitmer and P. Gilsanz contributed to the conception and design of the study. P. Gilsanz was responsible for the statistical analysis. All coauthors interpreted the data and contributed significantly to the manuscript.

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