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Clinically significant cognitive impairment in older adults with type 1 diabetes

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ABSTRACT

Aims: Little is known about cognition in older adults with type 1 diabetes. The aim of this study was to identify correlates of clinically significant cognitive impairment.
Methods: Neuropsychological, diabetes-related and glycemic (HbA1c, Continuous Glucose Monitoring; CGM) data were collected from 201 older adults (≥60 years) with longstanding type 1 diabetes.
Results: Clinically significant cognitive impairment (≥2 cognitive tests ≥1.5 SD below normative data) occurred in 48% of the sample. After controlling for age, gender, education and diabetes duration, we found that hypoglycemia unawareness, recent severe hypoglycemic events, any microvascular complication, higher HbA1c and CGM average nocturnal glucose were all associated with increased odds of clinically significant cognitive impairment (ORs = 1.01–2.61), while CGM nocturnal % time below 60 mg/dL was associated with a decreased odds of cognitive impairment (OR = 0.94). Diabetes duration, diagnosis age, daytime CGM, and lifetime severe hypoglycemic events were not related to cognitive impairment status.
Conclusions: Clinically significant cognitive impairment was common in older adults with type 1 diabetes. Diabetes-related correlates of cognitive impairment were identified, including hypoglycemia unawareness, recent severe hypoglycemic events, and CGM variables. Longitudinal research is needed to determine if these variables predict cognitive decline and if their modification alters outcomes.

1. Introduction

The population of older adults with type 1 diabetes is increasing due to a rising disease incidence (particularly in adults), reduced or delayed complications due to improved diabetes care, and longer life expectancy [1–4]. Given that older adults are at increased risk for declining cognition (e.g., normal aging, mild cognitive impairment, and dementia), it is important to determine if type 1 diabetes is associated with greater cognitive impairment than expected due to aging alone and if so, what diabetes-related and other risk factors are associated with cognitive impairment.

While there are known associations between type 2 diabetes, cognitive decline and dementia [5–12], the risk factors for, and the severity of cognitive impairment in adults with type 1 diabetes are less clear. An early meta-analysis of 33 studies demonstrated that compared to controls, younger adults (mean age = 33 years) with type 1 diabetes performed more poorly in the domains of intelligence, information processing speed, psychomotor efficiency, attention, cognitive flexibility and visual perception (d = 0.3 to 0.7)[13]. Cognitive dysfunction was associated with microvascular complications but not prior severe hypoglycemic episodes or HbA1c. Subsequent studies, however, have found that severe hypoglycemia, longer diabetes duration, and earlier age of onset predict poorer cognitive performance [14–17]. There is speculation that the aging brain may be more vulnerable to severe hypoglycemia, with evidence from a sample of middle aged and older adults with type 1 diabetes (mean age 55) showing that recent episodes of severe hypoglycemia were associated with cognitive dysfunction [15].

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To date, only a single study has examined rates of clinically significant cognitive impairment. Nunley and colleagues defined cognitive impairment as performance ≥1.5 standard deviations below normative data on 2 or more tests and found that 28% of their sample of middle aged adults (mean age = 49 yrs) met criteria for impairment. The strongest diabetes-related predictors were higher mean HbA1c over the prior 14 years, as well as retinopathy and polyneuropathy measured 5 years prior [18].

Given the limited data on cognition in those over age 60, it is not fully known whether the mild cognitive dysfunction seen in many young adults with type 1 diabetes may subsequently worsen as people grow older (and develop aging related disorders, including cerebrovascular disease). Similarly, it is not known whether the risk factors for cognitive impairment in later life differ from those in younger adults, as suggested by some writers [19]. To our knowledge, no studies have reported the prevalence and correlates of clinically significant cognitive impairment in a cohort of older adults with type 1 diabetes.

The goal of the current study was to characterize the degree of cognitive dysfunction of older adults with longstanding type 1 diabetes, as well as identify biomedical factors associated with clinically significant cognitive impairment in this age group. We hypothesized that older adults with type 1 diabetes will have a high prevalence of clinically meaningful cognitive impairment, and that cognitive impairment will be associated with measures of glycemic control, the presence of microvascular complications, recent severe hypoglycemic events and diabetes duration, as suggested by prior research.

2. Material and methods

2.1. Procedure

The study was conducted at 18 diabetes centers participating in the T1D Exchange Clinic Network [20] and included 201 participants enrolled between August 2013 and April 2014. The study protocol was approved by the institutional review board at each investigational site, and individual participants gave written informed consent to participate in the study. All assessments were performed by trained examiners. A board certified clinical neuropsychologist (first author) trained and certified all examiners for cognitive testing and conducted random quality review of 10% of the test administrations. Training consisted of a general overview of test administration and standardization procedures, followed by detailed review and feedback of audiotaped practice test administration. Capillary blood glucose had to be >70 mg/dL in order to begin the cognitive testing. If blood glucose fell between 60 and 70 mg/dL, a 15 g carbohydrate snack was eaten and blood glucose was re-tested 15 min later. Testing commenced if blood glucose was >70 mg/dL and the participant felt well enough to complete cognitive testing. If blood glucose was <60 mg/dL testing was rescheduled for the next visit.

2.2. Participants

All participants ($n = 201$) had a clinical diagnosis of autoimmune type 1 diabetes treated with insulin, were ≥60 years old, and had diabetes duration of ≥20 years. The original sample was recruited as part of a T1D Exchange case-control study investigating factors associated with severe hypoglycemia [16]. As such, half of the sample had at least one severe hypoglycemic event in the prior 12 months, defined as an event requiring assistance of another person as a result of altered consciousness or confusion, to administer carbohydrate, glucagon, or other resuscitative actions. The other 50% of the sample had no severe hypoglycemic events in the past 3 years. All participants were community dwelling older adults. For the current study, cases and controls were pooled in order to explore the relationships between cognition and demographic, diabetes-related and glycemic factors in older adults with type 1 diabetes. Exclusion criteria included: current home use of continuous glucose monitoring (CGM), chronic kidney disease stage 4 or 5 [glomerular filtration rate <30 mL/min/1.73 m^2 (if known)], prior clinical diagnosis of dementia, serious illness with life expectancy <1 year and history of pancreatic transplant.

2.3. Neuropsychological assessment

Participants were administered the following battery of neuropsychological measures: Symbol Digit Modalities Test (SDMT) [21], Trail Making Test (TMT) [22], Hopkins Verbal Learning Test-Revised (HVLT-R)[23], and the Grooved Pegboard Test (GPT) [24]. This battery was selected for brevity and sensitivity to the cognitive effects of aging and type 1 diabetes. All measures were appropriate for use with older adults. The SDMT oral and written, TMT A and B, HVLT-R total learning, delayed recall, and recognition, and GPT dominant and nondominant hand performances were converted into standardized scores (T-scores with a mean of 50 and standard deviation of 10, with lower scores reflecting poorer cognitive performance) corrected for age and/or education based on available normative data [age and education for SDMT, see [21]; age and education for TMT, see [25]; age for HVLT-R, see [23]; age for GPT, see [24]). Dichotomous variables were then created to classify individual test performances as "impaired" when performance fell 1.5 standard deviations or more below published normative data (T Score ≤35). The SDMT was considered impaired if either the written or the oral trial was impaired. Likewise, the GPT was considered impaired if either the dominant or nondominant hand was impaired. Participants with 2 or more impaired test performances (out of 7) were classified as having clinically significant cognitive impairment for subsequent analyses. This approach is similar to that used by Nunley et al. [18] to define participants with clinically relevant cognitive impairment and is aligned with diagnostic strategies for identifying Mild Cognitive Impairment [26].

Demographic and diabetes-related (e.g., sex, education, age, diabetes duration, age of diagnosis) variables, microvascular complications (retinopathy, neuropathy and nephropathy), glycemic control (HbA1c, blinded CGM for 2 weeks), recent severe hypoglycemic events (within the past 12 months), hypoglycemia unawareness, depression symptoms and functional status were collected in order to describe the sample, and/or test for associations with cognitive impairment. HbA1c was collected via central lab, microvascular complications were collected via medical record review concurrent with the study visit, history of severe hypoglycemic events was collected via interview and depression (Geriatric Depression Scale-15; [27]) and instrumental activities of daily living (Functional Activities Questionnaire; FAQ) [28]) were collected via self-report questionnaire. Hypoglycemia unawareness was defined as responding in the affirmative to the following question: "Have you lost some of the symptoms you used to have when your blood sugar is low?" (Question #2 from the Clarke Survey [29]). This method was chosen because several of the Clarke survey items ask about the occurrence of severe hypoglycemic events, which overlaps with our severe hypoglycemia variable. In addition, a single question method to ascertaining hypoglycemia unawareness has been validated against the full Clarke survey [30]. The Dexcom SEVENPLUS CGM was used in blinded mode for 14 days (2 sensors). CGM metrics included in the current study were average blood glucose, percent time below 60 mg/dL, and percent time above 180 mg/dL. Additional CGM variables for daytime and nighttime hours (midnight to 6:00 am) were also calculated since daytime self-management may be differentially related to cognitive impairment than glucose control while sleeping. More detail on the study methods and assessments are described elsewhere [16].

2.4. Statistical analysis

Between group (Normal Cognition vs Clinically Significant Cognitive Impairment) characteristics were compared using the Independent-samples *t*-test, Fisher's exact test and Mann-Whitney *U* test, as applicable. One sample *t*-tests were used to compare mean individual

Table 1
Demographic characteristics of participants by cognitive impairment status.[a]

			Not Impaired (N = 105)	Impaired (N = 96)	Total (N = 201)	p-Value
Age	Mean (years)		68.71	67.83	68.29	n.s. †
	Standard deviation		5.82	6.49	6.15	
Gender	Male	N (%)	52 (50%)	54 (56%)	106 (53%)	n.s. ‡
	Female	N (%)	53 (50%)	42 (44%)	95 (47%)	
Education†	High school or less	N (%)	9 (9%)	16 (17%)	25 (13%)	n.s. ‡
	Some college or college degree	N (%)	67 (64%)	57 (59%)	124 (62%)	
	Graduate degree	N (%)	29 (28%)	21 (22%)	50 (25%)	
Race/ethnicity	Non-Hispanic White	N (%)	100 (95%)	85 (89%)	185 (92%)	n.s. ‡
	Other race/ethnicity	N (%)	5 (5%)	11 (11%)	16 (8%)	

Significance denotes independent samples t-tests († parametric) for continuous data and X^2 tests (‡) for categorical data comparing cognitively impaired vs. not impaired groups.
[a] Cognitive impairment is defined as performance ≥1.5 SD below demographically corrected normative data on two or more neuropsychological tests.

neuropsychological performance to published demographically corrected normative data. Variables that significantly differed between groups in univariate analyses were entered as predictors in binary logistic regression models predicting group status (Normal Cognition vs. Clinically Significant Cognitive Impairment). Six separate logistic regression models were calculated for each predictor variable (CGM nocturnal % time <60 mg/dL, CGM average nocturnal glucose, HbA1c, recent severe hypoglycemic events, hypoglycemia unawareness, and microvascular complications), adjusted for age, education, gender and diabetes duration. Bonferroni correction ($p < 0.008$) was used to indicate significance for these analyses (0.05/6 separate logistic regression models). Finally, a model including all 6 predictors (adjusted for age, education, gender and diabetes duration) was also calculated in order to determine the unique contribution of each variable.

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA). Unless otherwise noted, all *p*-values are two-sided and $p \leq 0.05$ was used to indicate statistical significance.

3. Results

3.1. Demographic characteristics

Demographic characteristics of the cohort are given in Table 1. Median (interquartile range [IQR]) age at study entry was 66 (63–71) years ranging from 60 to 86, median (IQR) diabetes duration was 39 (29–50) years ranging from 20 to 73, and median (IQR) age at diabetes diagnosis was 30[17–37] years ranging from 5 to 57 years. The majority of the sample (74%) was diagnosed in adulthood (1% <7 years old and 26% <18 years old at diagnosis), which is reflective of the older adult population in the T1D Exchange as a whole. One hundred and eighty-five (92%) subjects were non-Hispanic white, 95 (47%) were female and 62% had at least some college education. One hundred and ninety-two (96%) participants scored within normal limits (raw score <8) on a measure of instrumental activities of daily living (Functional Activities Questionnaire). Twelve percent of the sample reported elevated depression symptoms on the Geriatric Depression Scale-15 using a cut-off score >5 [31].

3.2. Impairment on individual neuropsychological tests

Performance ≥1.5 SD below the mean of published demographically corrected normative data for each test was used as a cut-off to indicate impaired test performance. As a point of reference, scores ≥1.5 SD below the mean occur in 7% of the normal older adult population. The frequency of impairment on each individual neuropsychological test in our sample was 2–5 times that expected in an age (and education for TMT and SDMT) matched normal population (Table 2) using available published normative data for each test. The prevalence of impairment was highest on a test of executive functioning (i.e., Trails B = 38.6% impaired) and lowest on verbal recognition memory (i.e., HVLT-R recognition memory = 14.1% impaired). All test performances except Trail Making Test Part A differed significantly from published normative data (one sample *t*-test, see Table 2), with Cohen's effect sizes ranging from −0.13 to −1.05 (average effect size = −0.56).

3.3. Clinically significant cognitive impairment

The remaining analyses were focused on factors associated with the presence of clinically significant cognitive impairment (defined as 2 or more test performances ≥1.5 SD below the mean based on published normative data) in our sample, similar to the approach used by Nunley et al. [18]. Forty-eight percent ($n = 96$) had clinically significant cognitive impairment, while 52% did not ($n = 105$). As expected, all the individual neuropsychological test scores were significantly lower in those with clinically significant cognitive impairment compared to those with normal cognition, differing by 0.5–1.5 standard deviations (data not shown). The cognitive test battery was brief and not designed to differentiate amnestic from non-amnestic mild cognitive impairment. However, post-hoc analysis of cognitive impairment profiles revealed that only 12.5% of those with clinically significant cognitive impairment had impairment in memory alone (impaired on HVLT-R Total Recall,

Table 2
Neuropsychological performance compared to demographically adjusted normative data.

Neuropsychological test	N	Raw mean	Raw SD	T-score mean	T-score SD	t[a]	*p*	Effect size	% impaired[b]
HVLT-R total recall	200	22.82	5.37	44.46	10.78	−7.27	0.000	−0.55	21.5
HVLT-R delayed recall	199	7.77	3.16	44.86	12.76	−5.68	0.000	−0.51	20.6
HVLT-R recognition	199	9.97	2.08	47.22	13.36	−2.94	0.004	−0.28	14.1
SDMT oral (# correct)	190	44.53	11.57	43.54	9.73	−9.15	0.000	−0.65	21.1
SDMT written (# correct)	191	39.15	10.72	45.30	10.33	−6.29	0.000	−0.47	17.8
Trail making test A (sec)	199	38.40	14.58	48.69	13.18	−1.40	0.162	−0.13	15.6
Trail making test B (sec)	197	115.11	75.92	39.51	15.50	−9.50	0.000	−1.05	38.6
Grooved pegboard dominant hand (sec)	199	103.85	39.60	41.82	12.98	−8.89	0.000	−0.82	28.6
Grooved pegboard non-dominant hand (sec)	197	115.59	44.48	41.43	11.50	−10.47	0.000	−0.86	28.4

Note: HVLT-R = Hopkins Verbal Learning Test – Revised, SDMT = Symbol Digit Modalities Test.
[a] One sample T-test using 50 as the test value (mean t-score of normative data).
[b] Impaired = T-score of ≤35; 7% of the demographically matched normative sample performs at or below this threshold.

Table 3
Clinical and diabetes-related characteristics of participants by cognitive impairment status.[a]

			Not Impaired (N = 105)	Impaired (N = 96)	Total (N = 201)	p-Value
Diabetes duration	Mean (years)		39.02	40.23	39.60	n.s. †
	Standard deviation		12.76	10.53	11.73	
Age at diagnosis	Mean (years)		29.26	27.16	28.25	n.s. †
	Standard deviation		13.30	12.03	12.72	
Body mass index[b,c]	Mean		27.16	26.72	26.95	n.s. †
	Standard deviation		5.07	4.30	4.71	
Microvascular complications[d,c]	None	N (%)	54 (55%)	34 (38%)	88 (47%)	0.044 ‡
	1	N (%)	33 (34%)	33 (37%)	66 (35%)	
	2	N (%)	9 (9%)	16 (18%)	25 (13%)	
	3	N (%)	2 (2%)	6 (7%)	8 (4%)	
Hypo unaware	Yes	N (%)	56 (53%)	68 (71%)	124 (62%)	0.011 ‡
	No	N (%)	49 (47%)	28 (29%)	77 (38%)	
Severe hypo life	0	N (%)	10 (10%)	8 (10%)	18 (10%)	n.s. ‡
	1	N (%)	11 (11%)	7 (8%)	18 (10%)	
	2–4	N (%)	11 (11%)	14 (17%)	25 (14%)	
	5–9	N (%)	21 (21%)	12 (14%)	33 (18%)	
	10–19	N (%)	11 (11%)	17 (20%)	28 (15%)	
	20+	N (%)	37 (37%)	25 (30%)	62 (34%)	
Severe hypo last year	0	N (%)	64 (61%)	36 (38%)	100 (50%)	0.005 ‡
	1	N (%)	16 (15%)	17 (18%)	33 (16%)	
	2	N (%)	12 (11%)	13 (14%)	25 (12%)	
	3+	N (%)	13 (12%)	30 (31%)	43 (21%)	

Significance denotes independent samples t-tests († parametric) for continuous data and X^2 tests (‡) for categorical data comparing cognitively impaired vs. not impaired groups.
[a] Cognitive impairment is defined as performance ≥1.5 SD below demographically corrected normative data on two or more neuropsychological tests.
[b] Weight in kg divided by height in meters^2.
[c] BMI data missing for 4; Complications data missing for 14 (7 not impaired, 7 impaired).
[d] Microvascular complications include: Retinopathy, nephropathy, and neuropathy.

Delayed Recall and/or Recognition), while 44% had impairment on only processing speed/executive functioning tests (impaired on SDMT, Trails A and/or Trails B), and the remaining 44% had impairment in both domains. As can be seen in Table 1, there were no significant differences between the groups in age, gender, education or race/ethnicity. Depressive symptoms did not differ between those with cognitive impairment (median = 1) and those without (median = 1), U = 4188.5, $p > 0.05$.

Our data show univariate associations between the presence of cognitive impairment and some diabetes-related variables (Table 3). Those with at least 1 of 3 microvascular complication, two or more severe hypoglycemic events in the past year, and those with hypoglycemia unawareness were more likely to be cognitively impaired than those without these factors. There was no association between lifetime severe hypoglycemic events and cognitive impairment status. There was also no association between cognitive impairment status and diabetes duration, age at diagnosis, or body mass index.

In terms of glycemic differences (Table 4), those with clinically significant cognitive impairment had a significantly higher HbA1c than those without cognitive impairment, $t(198) = -0.27$, $p < 0.05$, although the magnitude of the difference was small (0.4%; 4.4 mmol/mol). CGM mean glucose, percent time above 180 mg/dL, percent time below 60 mg/dL, and glycemic variability (measured by the coefficient of variability) did not differ between cognitive impairment groups. CGM mean glucose at night was higher in those with cognitive impairment (Mean = 172 mg/dL) than those without (Mean = 158 mg/dL), $t(191) = 2.46$, $p < 0.05$. Those with cognitive impairment spent less time below 60 mg/dL at night (Median = 2.3%) than those without cognitive impairment (Median = 4.9%), $p < 0.05$.

Odds ratios were calculated for clinically significant cognitive impairment status using binary logistic regression adjusted for age, education, gender and diabetes duration (Table 5). Hypoglycemia unawareness, recent severe hypoglycemic events, any microvascular complication, higher HbA1c, and higher CGM average nocturnal glucose were all individually associated with increased odds of clinically significant cognitive impairment (ORs = 1.01 to 2.61). Greater CGM nocturnal percent time below 60 mg/dL was associated with a decreased

Table 4
Glycemic characteristics of participants by cognitive impairment status.[a]

		Not Impaired (n = 105)	Impaired (n = 96)	Total (n = 201)	p-value
HbA1c[b]	Mean % (mmol/mol)	7.56(59)	7.96(63)	7.75(61)	0.017 †
	SD % (mmol/mol)	1.12(12.2)	1.21(13.2)	1.18(12.9)	
CGM mean glucose	Mean (mg/dL)	171	180	175	n.s. †
	Standard Deviation	31	34	33	
CGM mean glucose at night	Mean (mg/dL)	158	172	165	0.015 †
	Standard Deviation	40	40	40	
CGM above 180 mg/dL	Median (percent time)	39.0	44.5	41.0	n.s. §
	IQR	27.0	27.0	27.0	
CGM above 180 mg/dL at night	Median (percent time)	31.0	38.5	34.0	n.s. §
	IQR	30.0	30.0	31.0	
CGM below 60 mg/dL	Median (percent time)	4.4	3.6	3.8	n.s. §
	IQR	6.0	5.0	5.7	
CGM below 60 mg/dL at night	Median (percent time)	4.9	2.3	3.5	0.002 §
	IQR	12.3	7.8	10.3	

Significance denotes independent samples t-tests (†parametric or § nonparametric) for continuous data.
[a] Cognitive impairment is defined as performance ≥1.5 SD below demographically corrected normative data on two or more neuropsychological tests.
[b] HbA1c missing for 1.

Table 5
Adjusted odds ratio estimates from logistic regression models examining the association between diabetes-related risk factors and clinically significant cognitive impairment.

	Adjusted[a] OR (95% CI)	*p*-Value
CGM percent time <60 mg/dL at night[b]	0.94 (0.90, 0.98)	**0.004**
CGM average glucose at night	1.01 (1.002, 1.02)	0.017
HbA1c	1.34 (1.05, 1.72)	0.021
Hypoglycemia unawareness[b]	2.14 (1.16, 3.92)	0.014
Severe hypoglycemic events in the last year (0–1 vs 2+ events)[b]	2.61 (1.40, 4.85)	**0.003**
Presence of one or more microvascular complication (retinopathy, neuropathy and/or nephropathy)	1.89 (1.04, 3.45)	0.037

Note: Bolded p-values are statistically significant after correction for multiple comparisons (Bonferroni corrected $p < 0.008$).
[a] Adjusted model accounts for the effects of age, gender, education and diabetes duration.
[b] Remained a significant predictor when all independent variables were included in the model together.

odds of cognitive impairment (OR = 0.94). When these independent variables were entered together into a single logistic regression model (again controlling for age, gender, education and diabetes duration) only hypoglycemia unawareness (OR = 2.23, 95% CI = 1.09, 4.53), recent severe hypoglycemic events (OR = 2.41, 95% CI = 1.18, 4.94), and percent time below 60 mg/dL (OR = 0.92, 95% CI = 0.87, 0.98) remained significant unique predictors of cognitive impairment.

4. Discussion

Our data demonstrate that community dwelling, non-demented, older adults with type 1 diabetes have a high prevalence of clinically significant cognitive impairment across a battery of neuropsychological tests. When looking at overall performance, *48% of the sample was impaired* (≥1.5 SD below the mean) on 2 or more neuropsychological tests, despite the vast majority having no impairment in activities of daily living, a presentation consistent with mild cognitive impairment. As a point of reference, approximately 16% of adults over age 60 meet criteria for a clinical diagnosis of mild cognitive impairment[32]. We found nearly twice the frequency of clinically significant cognitive impairment compared to middle aged adults with type 1 diabetes (28% impaired[18]) and 8 times that found in adolescents (6% impaired[33]) using similar methodology. Higher rates of cognitive impairment in older samples could indicate decline in cognition from childhood to middle age to older adulthood, although our cross-sectional data does not allow for direct comparisons. Longitudinal data are needed to determine if the cognitive impairment reported here is static or will continue to worsen over time, and if worsening, at what rate. It also is important to identify risk factors that predict future cognitive decline in this population, as this will allow for proactive interventions that may stave off cognitive decline before it occurs.

Similar to findings in samples of younger adults with type 1 diabetes, those with clinically significant cognitive impairment in our study were more likely to have a higher HbA1c and at least one microvascular complication (retinopathy, nephropathy and/or neuropathy), although diabetes duration and age of diagnosis did not differ between groups in our sample. This latter finding may be due to the fact that the majority of our sample was diagnosed in adulthood, thus eliminating the effect of diabetes on the developing brain and long term effects of poorer glycemic control often seen in adolescence. It should be noted that the age of onset of our sample (74% diagnosed over age 18) is reflective of the broader population of older adults with type 1 diabetes in the T1D Exchange Clinic Registry (1725/2355 or 73%, based on data available via the T1D Exchange Clinic Registry online discovery tool: https://t1dexchange.org/pages/resources/our-data/t1d-discover/).

We found that lifetime frequency of severe hypoglycemic events was not associated with cognitive impairment, consistent with findings from the Diabetes Control and Complications Trial and later follow-up that did not find greater cognitive decline in those with a history of severe hypoglycemic episodes over an 18-year period[34]. However, we did find that two or more severe hypoglycemic events in the past year increased risk for cognitive impairment. This is consistent with two other studies showing that recent severe hypoglycemic events may be a risk factor for cognitive decline in older adults specifically [15,35]. In fact, it has been hypothesized that neurodegeneration associated with aging (along with brain development in childhood) represents "a crutial period" when the brain is more vulnerable to the effects of severe hypoglycemia compared to middle age [19]. While it may make intuitive sense to assume that recent severe hypoglycemic events result in brain damage that leads to cognitive impairment in older adults due to vulnerability of an aging brain, it is also plausible that cognitive decline associated with aging or other age-related conditions increases the likelihood of making a self-management error that leads to a severe hypoglycemic event [36,37].

Those with cognitive impairment were also more likely to have hypoglycemia unawareness, compared to those without clinically significant cognitive impairment. This relationship was independent of recent severe hypoglycemic events and nocturnal CGM percent time below 60 mg/dL. This finding is consistent with a recent study from Norway showing that middle aged adults with type 1 diabetes and hypoglycemia unawareness were more cognitively impaired relative to matched type 1 diabetes controls with normal hypoglycemia awareness [38]. They found no association between cognitive performance and prior severe hypoglycemic events (in the last year or lifetime). It is possible that cognitive impairment results in a reduced ability to monitor, detect or interpret the early signs of hypoglycemia, and/or react appropriately to avoid severe hypoglycemia. It is also possible that the neurological changes associated with hypoglycemia unawareness also adversely affect higher level cognitive functions.

We found associations between some, but not all CGM variables. Those with cognitive impairment had higher mean CGM glucose at night (but not during the day), consistent with prior data linking higher HbA1c to greater cognitive impairment, as well as emerging data linking CGM metrics with cognitive performance in patients with type 2 diabetes [39,40]. Those who spent more time below 60 mg/dL at night on blinded CGM were less likely to be cognitively impaired. Similar results were found when thresholds of below 70 mg/dL (OR = 0.96, 95% CI = 0.93, 0.99) or below 50 mg/dL (OR = 0.93, 95% CI = 0.88, 0.98) were used, and when this variable was dichotomized to compare those with >30 min below 60 mg/dL (OR = 0.44, 95% CI = 0.22, 0.86). Because these data are cross-sectional, it is impossible to determine the direction of these associations. It is possible that individuals with cognitive impairment have higher self, family or physician imposed blood glucose targets in an attempt to minimize hypoglycemia, whereas those with good cognitive functioning may feel more confident setting lower blood glucose targets (with associated risk for lower blood glucose at night). In support of this, those with higher nocturnal percent time below 60 mg/dL had lower HbA1c ($r = -0.22$, $p < 0.05$). Since we also found that severe hypoglycemic events in the past year were associated with cognitive impairment, it may be that those with cognitive impairment are less able to respond appropriately when mild hypoglycemia occurs, and ultimately experience an episode of more severe hypoglycemia. In contrast, despite experiencing more mild hypoglycemia overall, those without cognitive impairment may be able to avoid severe hypoglycemia more effectively in the setting of mild hypoglycemia. We are not aware of any existing data linking CGM metrics with cognitive

performance in type 1 diabetes, or data that nocturnal blood glucose is preferentially linked to cognitive performance, making it critical that these findings are replicated.

There are several limitations of this study. First, our sample was overwhelmingly Caucasian and highly educated, and as such, these results may not generalize to others with type 1 diabetes. The demographic make-up of our study is, however, highly consistent with the population of older adults in the Type 1 Diabetes Exchange Clinic Registry from which our sample was drawn [41]. Our subjects were originally recruited for a case control study with half of the participants being selected for a recent history of severe hypoglycemic episodes, and as such, it is not a representative sample of older adults with type 1 diabetes (~18% of older adults with type 1 diabetes has had severe hypoglycemia in the past year [41]). While this maximized our power to detect findings related to the relationship between recent severe hypoglycemia and cognitive impairment, our design may have also led to a higher rate of clinically significant cognitive impairment in our sample than would be seen in the general populations of older adults with type 1 diabetes. However, even among those with no severe hypoglycemia in the past 3 years ($N = 100$), clinically significant cognitive impairment was higher than expected (36% impaired). Lastly, our sample had an average diabetes onset in adulthood, with very few being diagnosed before age 7. While this may limit comparisons to other type 1 diabetes cohorts with childhood onset, it has advantages as well, since this removes the possible impact of type 1 diabetes on neurodevelopmental processes.

We previously reported that neuropsychological impairment is associated with the complex mental operations required for successful diabetes self-management tasks in this sample of older adults [37]. Clinicians are encouraged to routinely screen older adults with type 1 diabetes for mild cognitive impairment as recommended by the American Diabetes Association [42] and if present, to implement individualized strategies for reducing risk and maximizing functional independence. However, common dementia screening tools that emphasize memory impairment (e.g., mini-cog, Mini-mental Status Examination) may fail to identify the type of cognitive impairment most commonly found in older adults with type 1 diabetes (processing speed and executive function). More work is needed to identify more appropriate screening tools.

Future research is needed to determine the efficacy of diabetes self-management interventions that are tailored to older adults with cognitive impairment, such as training in the use of compensatory strategies and environmental aids to assist with common diabetes-related tasks. Compensatory diabetes-self-management strategies should emphasize "time out" procedures, taking extra time to make diabetes-related decisions, and decision support given the cognitive profile most commonly observed here (i.e., processing speed/executive dysfunction rather than isolated memory impairment). In addition, formal assessment of the effectiveness of CGM (with or without alarms for hypoglycemia) for preventing severe hypoglycemia in older adults with cognitive impairment is needed. Longitudinal research designs are also needed to determine if the cross-sectional associations reported here are associated with cognitive change over time, and whether it is possible to reduce risk for cognitive decline via modification of these variables (e.g., do interventions that reduce severe hypoglycemia or hypoglycemia unawareness, also reduce cognitive decline). Lastly, research combining neuropsychological assessment with neuroimaging may be able to further elucidate underlying mechanisms of cognitive impairment in older adults with type 1 diabetes.

In conclusion, as the population of older adults with type 1 diabetes continues to increase over time, so too will the burden of cognitive impairment. Nearly 50% of adults over age 60 with type 1 diabetes met our criteria for clinically significant cognitive impairment, with microvascular complications, higher HbA1c and average nocturnal CGM glucose, hypoglycemia unawareness and recent severe hypoglycemic events being associated with increased risk. Nocturnal CGM hypoglycemia, which may be a surrogate of better metabolic control, was associated with lower risk. Longitudinal research is needed to determine if these variables predict cognitive decline over time and if their modification alters outcomes.

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