

Comparison of cognitive function in older adults with type 1 diabetes, type 2 diabetes, and no diabetes: results from the Study of Longevity in Diabetes (SOLID)

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ABSTRACT

Introduction The incidence of both type 1 diabetes (T1D) and type 2 diabetes (T2D) is increasing. Life expectancy is improving in T1D, resulting in a growing population of elderly adults with diabetes. While it is well established that older adults with T2D are at increased risk of cognitive impairment, little is known regarding cognitive aging in T1D and how their cognitive profiles may differ from T2D.

Research design and methods We compared baseline cognitive function and low cognitive function by diabetes status (n=734 T1D, n=232 T2D, n=247 without diabetes) among individuals from the Study of Longevity in Diabetes (mean age=68). We used factor analysis to group cognition into five domains and a composite measure of total cognition. Using linear and logistic regression models, we examined the associations between diabetes type and cognitive function, adjusting for demographics, comorbidities, depression, and sleep quality.

Results T1D was associated with lower scores on total cognition, language, executive function/psychomotor processing speed, and verbal episodic memory, and greater odds of low executive function/psychomotor processing speed (OR=2.99, 95% CI 1.66 to 5.37) and verbal episodic memory (OR=1.92, 95% CI 1.07 to 3.46), compared with those without diabetes. T2D was associated with lower scores on visual episodic memory. Compared with T2D, T1D was associated with lower scores on verbal episodic memory and executive function/psychomotor processing speed and greater odds of low executive function/psychomotor processing speed (OR=1.74, 95% CI 1.03 to 2.92).

Conclusions Older adults with T1D had significantly poorer cognition compared with those with T2D and those without diabetes even after accounting for a range of comorbidities. Future studies should delineate how to reduce risk in this vulnerable population who are newly surviving to old age.

INTRODUCTION

In recent decades, diabetes has emerged as a significant risk factor for dementia. Among individuals with diabetes, the risk of developing dementia is two times higher than in

Significance of this study

What is already known about this subject?

- In individuals with type 1 diabetes (T1D) and type 2 diabetes (T2D), studies have consistently shown mild to modest cognitive deficits on a range of neurocognitive tests as compared with individuals without diabetes.
- There are limited studies examining cognitive function in older adults with T1D.

What are the new findings?

- In this study of older adults with T1D, T2D, and without diabetes, we found significantly poorer cognitive function in those with T1D as compared with those with T2D and compared with those without diabetes.
- Those with T1D had lower scores on total cognition, language, executive function/psychomotor processing speed, and verbal episodic memory, and greater odds of low executive function/psychomotor processing speed and verbal episodic memory, compared with those without diabetes.
- Compared with T2D, T1D was associated with lower scores on language, verbal episodic memory, and executive function/psychomotor processing speed, and greater odds of low executive function/psychomotor processing speed.

How might these results change the focus of research or clinical practice?

- As more individuals with T1D reach older adulthood, it is crucial to understand the aging-related challenges they may face.
- Our findings underscore the importance of close monitoring of cognitive function in older adults with T1D as they enter older adulthood.

those without diabetes.^{1–3} With few exceptions, however, the majority of studies on which these estimates are based have been conducted among older adults with type 2 diabetes (T2D). There is little known about

the risk of dementia in type 1 diabetes (T1D); however, from the few available studies, evidence seems to suggest that T1D may also be associated with an increased risk of dementia.^{4–7} The lack of attention given to risk of dementia in T1D is likely attributable, in part, to the shortened life expectancy among those with T1D and few longitudinal cohorts. However, with advances in treatment, individuals with T1D are experiencing increased life expectancy, resulting in a growing population of adults with T1D living into old age.^{8–10} As more individuals with T1D reach older adulthood, it is crucial to understand aging-related challenges they may face.

In individuals with T1D and T2D, studies have consistently shown mild to modest cognitive deficits on a range of neurocognitive tests as compared with individuals without diabetes. In T2D, deficits are reported in middle and older adults alike and are observed on a number of cognitive domains, including episodic memory, information processing speed, attention, and executive function.^{11–14} In T1D, cognitive deficits are also well documented; however, with few exceptions, the majority of studies have been conducted in middle-aged adults or younger. In young and middle-aged adults with T1D, studies consistently report cognitive deficits in executive function^{15–16} and verbal intelligence,^{17–18} with the most pronounced differences observed in those with earlier age of disease onset and those with exposure to hypoglycemia or diabetic ketoacidosis (DKA).^{19–23} Deficits in these domains are especially important as they can impact an individual's ability to effectively manage their disease. Studies characterizing cognitive function in younger and middle-aged adults with T1D have reported cognitive decline or poorer cognitive function associated with cardiovascular events, severe hypoglycemic events, recurrent DKA, or chronic hyperglycemia.^{24–28} Despite these few studies, it remains unclear how these cognitive deficits observed earlier in life impact an aging population of adults with T1D and how they may or may not differ from aging individuals with T2D. Understanding cognitive performance in those aging with T1D can provide unique insights into relative contributions of T1D to the risk of dementia and help delineate some of the mechanisms underlying this increased risk prior to the development of frank dementia. This is especially important given older adults with T1D are unique in many ways compared with older adults with T2D. In addition to differences in the etiology and causes of T1D versus T2D, those with T1D have a younger age of onset of disease, longer disease duration, and continuous insulin treatment since diagnosis, and are two to three times more likely to have severe hyperglycemic crises, severe hypoglycemia, and impaired awareness of hypoglycemia.^{29–31}

In the current study, we compare cognitive function, evaluated using a comprehensive battery of cognitive tests, among 1241 adults aged ≥ 60 years with T1D ($n=762$), T2D ($n=232$), or without diabetes ($n=247$). Differences in cognitive performance and prevalence of low cognitive function among those with T1D or T2D compared

with those without diabetes are examined in models with varying levels of adjustment for diabetes complications and a range of comorbidities. We also directly compare cognitive function and low cognitive function among older adults with T1D and those with T2D.

RESEARCH DESIGN AND METHODS

Study population

The Study of Longevity in Diabetes (SOLID) is a prospective cohort study of aging and diabetes that recruited members of Kaiser Permanente Northern California (KPNC) aged ≥ 60 with T1D, T2D, and without diabetes. The present analysis focuses on baseline measures collected from August 2015 to June 2017. Details of participant eligibility and inclusion have been published previously.^{27–28} Briefly, eligible members with diabetes were identified using a validated algorithm based on International Classification of Diseases (ICD)-9 and ICD-10 diagnosis codes and medication orders extracted from their electronic medical records.^{32–33} Members were classified as having T1D if $\geq 75\%$ of their diabetes-related diagnostic codes were for T1D (250.x1, 250.x3, or E10.x) and they were prescribed insulin. Manual medical record review was conducted for participants reporting onset of T1D at ≥ 31 years of age to confirm T1D status. Members were classified as having T2D if $\geq 75\%$ of diabetes-related diagnostic codes were for T2D (250.x0, 250.x2, or E11.x). A total of 805 KPNC members with T1D aged ≥ 60 were enrolled and completed baseline interviews. Enrolled participants with T1D were then used to guide recruitment of two comparator groups: individuals with T2D and individuals without diabetes. Participants with T1D were population frequency-matched (on sex, age, race/ethnicity, and education) to potential participants with T2D and without diabetes. A total of 248 KPNC members with T2D and 258 without diabetes were enrolled and completed baseline interviews. All enrolled participants provided informed consent.

Cognitive function

All participants were administered a comprehensive cognitive battery by trained interviewers at their baseline interview. We conducted factor analysis on cognitive assessments from all participants through which five cognitive domains were identified: language, executive function/psychomotor processing speed, visual episodic memory, verbal episodic memory, and simple attention. The language domain included the phonemic fluency test (F and L), the category fluency test (animals and vegetables), list sorting (two alternative lists), and Multilingual Naming Test. The executive function/psychomotor processing speed domain included the Trail Making Test (A and B), the Digit Symbol Substitution Test, and the Stroop Color and Word Test. The verbal episodic memory domain included the Word List Learning Test (immediate and delayed). The visual episodic domain included the Benson Complex Figure

Copy (immediate and delayed). The simple attention domain encompassed the Diamond and TMX cancellation tests. For all tests except the Stroop Color and Word Test and the Trail Making Test (A and B), performance was assessed using the number of items correct; for the Stroop Color and Word Test and the Trail Making Test (A and B), performance was assessed using time to task completion. Each test score was converted to a z-score (mean=0, SD=1). A total cognition score was calculated as the average of the five domain-specific scores. Low total and domain-specific scores were defined as scores ≥ 1.5 SD below the mean of those without diabetes.

Covariates

Date of baseline interview and date of birth were used to calculate age. Age of diabetes onset was obtained via participant self-report and was used, in conjunction with age at baseline interview, to estimate diabetes duration. Sex was obtained from KPNC records. Race/ethnicity was based on self-report and was categorized into white, black, Hispanic, Asian, and other.

Educational attainment was based on self-report and was categorized as 'Some college or less', 'Bachelor's degree', or 'Graduate or professional degree'. The following baseline health conditions were based on self-reported history of a physician's diagnosis: retinopathy, neuropathy, nephropathy, stroke/cerebrovascular event, and myocardial infarction. Lifetime history of DKA and past 12-month history of severe hypoglycemia resulting in hospitalization were self-reported by those with T1D or T2D. Depression symptoms were assessed at baseline using the Geriatric Depression Scale (GDS), which is a 15-item measure of depression.³⁴ Each item on the GDS is scored with 1 point for a depressive response, with higher scores indicating more severe depression. Total depression score was used as a continuous covariate. The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality in participants.³⁵ The PSQI measures seven areas of sleep over the past month to differentiate between 'good' and 'poor' quality of sleep. Global PSQI scores range from 0 to 21, with higher scores indicating worse sleep quality. The PSQI was used as a continuous covariate. Blood glucose readings at baseline were available for participants who had a blood glucose monitor at the time of the interview or who had taken a reading that morning and were able to recall their blood glucose value.

Analytic sample

The present analysis uses baseline measures for participants with T1D, T2D, and those without diabetes from SOLID. Of the 1311 individuals who were enrolled and completed baseline measures (n=805 with T1D; n=248 with T2D; n=258 without diabetes), we excluded 70 participants who were missing the total cognition score, resulting in a final analytic sample of 1241. Of these 1241 participants, 750 (60%) had a recorded blood glucose value available at the start of the inperson interview (632

with T1D and 118 with T2D). Of the 750 with glucose values recorded at baseline, 23 had a blood glucose value <70 mg/dL and were excluded from all analyses given the possible transient effects of acute hypoglycemia on cognitive function, resulting in a final analytic sample of 1213. Online supplemental table 1 summarizes the characteristics of those who were excluded versus those who were included in the final analytic sample.

Statistical analyses

Participants' baseline characteristics were examined in the overall sample and were compared across categories of diabetes status (T1D, T2D, and no diabetes) using analysis of variance and χ^2 test.

For our main analysis, we used linear regression models to examine the association between diabetes type and cognitive function. To compare the association between diabetes type and cognitive function, we fit a set of models using people without diabetes as the reference group. First, we fit a base model (model 1) examining the association between diabetes type and cognition in which we adjusted for race/ethnicity, age, sex, and education. Next, we fit two models in which we additionally adjusted for microvascular and macrovascular complications (model 2a: model 1 + retinopathy, neuropathy, stroke, and myocardial infarction) and for measures of health status at baseline (model 2b: model 1 + GDS, PSQI, and body mass index) to understand the contribution of each of these factors to the association between diabetes and cognition. Nephropathy was not included in model 2a or model 3 to avoid potential positivity bias.³⁶ Positivity is the requirement that there are participants at every combination of values of covariates; there was only one participant with T2D and one participant without diabetes who reported nephropathy. Finally, we fit a fully adjusted model (model 3) controlling for all covariates from models 1, 2a, and 2b. In a sensitivity analysis to examine the potential influence of acute metabolic events (DKA or severe hypoglycemia) on cognition, we restricted our sample to those individuals with no history of acute metabolic events and fit the fully adjusted model.

Next, we fit a series of regression models in which we excluded those without diabetes and directly compared cognitive function in those with T1D to those with T2D (using the T2D group as the reference group). In this series of models, we followed the same covariate adjustment strategy outlined above, except in models 2 and 3 where we added current insulin use as a covariate.

As a secondary analysis, we defined low cognitive function using a cut-off of ≥ 1.5 SD below the mean of those without diabetes as a threshold. We then used multivariable logistic regression models (adjusting for age at baseline interview, sex, race/ethnicity, and education) to examine the odds of low cognitive function associated with T1D or T2D compared with those without diabetes, as well as the odds of low cognitive function associated with T1D compared with those with T2D (excluding

Table 1 Baseline characteristics of SOLID participants

| | Overall (N=1213) | T1D (n=734) | T2D (n=232) | No diabetes (n=247) | P value |
|--|---------------------|----------------|----------------|------------------------|---------|
| Overall sample | | | | | |
| Age at baseline, mean (SD) | 67.79 (6.60) | 67.20 (6.25) | 68.70 (7.04) | 68.70 (7.00) | <0.001 |
| Female, n (%) | 621 (51.20) | 376 (51.23) | 118 (50.86) | 127 (51.42) | 0.99 |
| Race/ethnicity, n (%) | | | | | <0.0001 |
| White | 1026 (84.58) | 621 (84.60) | 195 (84.05) | 210 (85.02) | |
| African American | 21 (1.73) | 21 (2.86) | 0 (0.00) | 0 (0.00) | |
| Asian | 21 (1.73) | 20 (2.72) | 1 (0.43) | 0 (0.00) | |
| Hispanic | 97 (8.00) | 28 (3.81) | 34 (14.66) | 35 (14.17) | |
| Mixed race/other | 44 (3.63) | 40 (5.45) | 2 (0.86) | 2 (0.81) | |
| Unknown | 4 (0.33) | 4 (0.54) | 0 (0.00) | 0 (0.00) | |
| Highest level of educational attainment, n (%) | | | | | 0.42 |
| Some college or less | 473 (38.99) | 276 (37.60) | 93 (40.09) | 104 (42.11) | |
| Bachelor's degree | 371 (30.59) | 239 (32.56) | 65 (28.02) | 67 (27.13) | |
| Graduate or professional degree | 365 (30.09) | 215 (29.29) | 74 (31.90) | 76 (30.77) | |
| BMI (kg/m ²), mean (SD) | 29.08 (6.33) | 27.65 (5.36) | 34.02 (7.76) | 28.66 (5.10) | <0.0001 |
| Geriatric Depression Scale, mean (SD) | 1.99 (2.27) | 2.14 (2.35) | 2.32 (2.51) | 1.21 (1.45) | <0.0001 |
| Pittsburgh Sleep Quality Index, mean (SD) | 8.02 (2.72) | 8.11 (2.81) | 8.21 (2.59) | 7.53 (2.51) | 0.01 |
| Stroke, n (%) | 99 (80.06) | 63 (8.58) | 20 (8.62) | 16 (6.48) | 0.48 |
| Myocardial infarction, n (%) | 122 (10.06) | 90 (12.26) | 22 (9.48) | 10 (4.05) | 0.001 |
| Retinopathy, n (%) | 333 (27.45) | 312 (42.51) | 19 (8.19) | 2 (0.81) | <0.0001 |
| Nephropathy, n (%) | 56 (4.62) | 54 (7.36) | 1 (0.43) | 1 (0.40) | <0.0001 |
| Neuropathy, n (%) | 364 (30.01) | 292 (39.78) | 56 (24.14) | 16 (6.48) | <0.0001 |
| Among those with diabetes only (n=966) | | | | | |
| Age at diabetes diagnosis, mean (SD) | 34.68 (18.49) | 28.29 (15.18) | 55.69 (10.82) | – | <0.0001 |
| Diabetes duration in years, mean (SD) | 32.93 (17.85) | 39.05 (15.05) | 13.06 (10.06) | – | <0.0001 |
| Current insulin use, n (%) | 810 (83.85) | 719 (97.96) | 63 (27.16) | – | <0.0001 |
| Severe hypoglycemia, n (%)* | 246 (25.47) | 220 (29.97) | 12 (5.17) | – | <0.0001 |
| Diabetic ketoacidosis, n (%)† | 207 (21.43) | 206 (29.43) | 1 (0.45) | – | <0.0001 |

*Severe hypoglycemia in the past 12 months.

†Lifetime diabetic ketoacidosis resulting in hospitalization.

BMI, body mass index; SOLID, Study of Longevity in Diabetes; T1D, type 1 diabetes; T2D, type 2 diabetes.

those without diabetes). All analyses were performed using SAS V.9.4.

RESULTS

Our sample of 1213 older adults included 734 participants with T1D, 232 with T2D, and 247 without diabetes. By design, the three groups were relatively comparable in terms of age, sex, race/ethnicity, and education status, although the mean age at baseline and the percent of participants with some college or less were slightly lower in those with T1D (table 1).

The average age at diabetes onset was 28.29 years (SD=15.18) in those with T1D compared with 55.69 years (SD=10.82) in those with T2D ($p<0.0001$). The average duration of diabetes was 39.05 years (SD=15.05) in T1D and 13.06 years (SD=10.06) in T2D ($p<0.0001$). Compared to people without diabetes, those with T1D or T2D were more likely to report a history of stroke and

myocardial infarction, and they had higher scores on the GDS and the PSQI, indicating more depressive symptoms and worse sleep quality, respectively. The rates of retinopathy, nephropathy, and neuropathy were highest in the T1D group, followed by T2D, and lowest in those without diabetes. Among those with T1D, 30% reported a history of severe hypoglycemia resulting in hospitalization in the past 12 months and 29% reported a lifetime history of DKA resulting in hospitalization; in T2D, 5% reported severe hypoglycemia in the past 12 months and <1% reported DKA.

Minimally adjusted regression models (table 2, model 1) revealed significant differences across multiple domains and on total cognition among those with either T1D or T2D compared with those without diabetes.

T1D was associated with worse total cognition as well as lower scores on the language, executive function/psychomotor processing speed, and verbal episodic memory

Table 2 Cognitive function in older adults with type 1 and type 2 diabetes compared with those without diabetes

| | Total cognition | | Language | | Executive function/ psychomotor processing speed | | Verbal episodic memory | | Visual episodic memory | | Attention | |
|---|-----------------|-------------------|----------|------------------|---|------------------|------------------------|------------------|------------------------|------------------|-----------|-----------------|
| | β | (95% CI) | β | (95% CI) | β | (95% CI) | β | (95% CI) | β | (95% CI) | β | (95% CI) |
| Model 1: adjusted for race/ethnicity, age, sex, and educational attainment | | | | | | | | | | | | |
| No diabetes | Ref | | Ref | | Ref | | Ref | | Ref | | Ref | |
| T1D | -0.14 | (-0.21 to -0.07) | -0.23 | (-0.32 to -0.14) | -0.35 | (-0.45 to -0.26) | -0.15 | (-0.27 to -0.03) | 0.11 | (0.01 to 0.22) | -0.07 | (-0.18 to 0.04) |
| T2D | -0.12 | (-0.20 to -0.04) | -0.11 | (-0.22 to -0.01) | -0.17 | (-0.29 to -0.06) | 0.01 | (-0.14 to 0.16) | -0.21 | (-0.33 to -0.08) | -0.10 | (-0.24 to 0.03) |
| Model 2a: model 1 + additional adjustment for stroke, MI, neuropathy, and retinopathy | | | | | | | | | | | | |
| No diabetes | Ref | | Ref | | Ref | | Ref | | Ref | | Ref | |
| T1D | -0.10 | (-0.17 to -0.03) | -0.19 | (-0.29 to -0.09) | -0.25 | (-0.35 to -0.15) | -0.17 | (-0.30 to -0.03) | 0.15 | (0.03 to 0.27) | -0.03 | (-0.15 to 0.09) |
| T2D | -0.10 | (-0.17 to -0.02) | -0.09 | (-0.20 to 0.02) | -0.12 | (-0.23 to -0.01) | 0.02 | (-0.13 to 0.16) | -0.19 | (-0.32 to -0.06) | -0.09 | (-0.22 to 0.05) |
| Model 2b: model 1 + additional adjustment for depression, PSQI, and BMI | | | | | | | | | | | | |
| No diabetes | Ref | | Ref | | Ref | | Ref | | Ref | | Ref | |
| T1D | -0.11 | (-0.18 to -0.05) | -0.21 | (-0.30 to -0.11) | -0.30 | (-0.40 to -0.20) | -0.14 | (-0.26 to -0.01) | 0.13 | (0.02 to 0.25) | -0.05 | (-0.17 to 0.07) |
| T2D | -0.08 | (-0.16 to 0.01) | -0.08 | (-0.20 to 0.04) | -0.10 | (-0.22 to 0.03) | 0.08 | (-0.08 to 0.24) | -0.19 | (-0.33 to -0.05) | -0.08 | (-0.23 to 0.07) |
| Model 3: adjustment for all covariates in models 1, 2a, and 2b | | | | | | | | | | | | |
| No diabetes | Ref | | Ref | | Ref | | Ref | | Ref | | Ref | |
| T1D | -0.08 | (-0.15 to -0.001) | -0.18 | (-0.28 to -0.08) | -0.21 | (-0.32 to -0.10) | -0.14 | (-0.28 to 0.003) | 0.17 | (0.05 to 0.29) | -0.01 | (-0.14 to 0.12) |
| T2D | -0.06 | (-0.15 to 0.02) | -0.06 | (-0.18 to 0.06) | -0.06 | (-0.18 to 0.06) | 0.08 | (-0.08 to 0.24) | -0.18 | (-0.32 to -0.04) | -0.07 | (-0.22 to 0.08) |

Linear regression models examining the association between diabetes type and cognitive function with varying levels of covariate adjustment.

Results in bold are statistically significant.

BMI, body mass index; MI, myocardial infarction; PSQI, Pittsburgh Sleep Quality Index; Ref, reference; T1D, type 1 diabetes; T2D, type 2 diabetes.

domains, but better performance on the visual episodic memory domain. All associations among T1D were attenuated, but remained statistically significant, with additional adjustment for microvascular and macrovascular complications (model 2a) and depression and sleep quality (model 2b). In fully adjusted linear regression models (model 3), compared with those without diabetes, individuals with T1D had poorer total cognitive function ($\beta=-0.08$, 95% CI -0.15 to -0.001), and lower scores on language ($\beta=-0.18$, 95% CI -0.28 to -0.08) and executive function/psychomotor processing speed ($\beta=-0.21$, 95% CI -0.32 to -0.10) domains, but performed better on the visual episodic memory domain ($\beta=0.17$, 95% CI 0.05 to 0.29). In minimally adjusted models (model 1), T2D was associated with worse total cognition and lower scores on the language, executive function/psychomotor processing speed, and visual episodic memory domains compared with those without diabetes. These associations were attenuated and in some cases were no longer significant after adjustment for depression and sleep quality at baseline (model 2a) and baseline comorbidities (model 2b). In fully adjusted models (model 3), those with T2D had poorer performance on the visual episodic memory domain only ($\beta=-0.18$, 95% CI -0.32 to -0.04).

To examine the potential influence of acute metabolic events on cognition, we conducted a sensitivity analysis to examine the association between diabetes type and cognitive function in a sample restricted to individuals with no lifetime history of DKA or past 12-month severe hypoglycemia resulting in hospitalization (online supplemental table 2); this subgroup included 371 with T1D (n=363 excluded), 219 with T2D (n=13 excluded), and 247 individuals without diabetes (n=0 excluded). Compared to those without diabetes, those with T1D had significantly lower scores on the language ($\beta=-0.14$, 95% CI -0.26 to -0.03) and executive function/psychomotor processing speed ($\beta=-0.14$, 95% CI -0.26 to -0.03) domains and significantly higher scores on the visual episodic domain ($\beta=0.19$, 95% CI 0.05 to 0.32). In this sensitivity analysis, the differences in cognitive function between those with T1D with no prior exposure to acute metabolic events and those without diabetes were smaller than the differences observed in the overall sample. Among those with T2D, the results were similar to those observed in the overall sample.

In fully adjusted linear regression models directly comparing cognitive function in those with T1D to those with T2D (table 3, model 3), individuals with T1D had poorer cognition on the executive function/psychomotor processing speed ($\beta=-0.14$, 95% CI -0.26 to -0.02) and verbal episodic memory ($\beta=-0.21$, 95% CI -0.37 to -0.06) domains and better cognition on the visual episodic memory domain ($\beta=0.36$, 95% CI 0.23 to 0.49). No difference was observed in total cognitive function in those with T1D compared with those with T2D.

In logistic regression models (table 4), using individuals without diabetes as the reference group, we observed increased odds of low cognitive function (defined as ≥ 1.5

SD below the mean of those without diabetes) in the T1D group for executive function/psychomotor processing speed ($\beta=2.99$, 95% CI 1.66 to 5.37) and verbal episodic memory (OR=1.92, 95% CI 1.07 to 3.46). No significant increase in risk of low cognitive function was observed for those with T2D on any domain in comparison with those without diabetes. In logistic regression models directly comparing those with T1D with those with T2D, individuals with T1D had greater odds of low cognitive function on the executive function/psychomotor processing speed domain only (OR=1.74, 95% CI 1.03 to 2.92).

CONCLUSIONS

In this study of 1213 older adults with T1D, T2D, and without diabetes, individuals with T1D had lower cognitive scores on a range of domains and were more likely to have low cognitive function on select domains as compared with those with T2D and those without diabetes. Compared with those with T2D, those with T1D had lower scores on language, verbal episodic memory, and executive function/psychomotor processing speed and were nearly two times more likely to have low executive function/psychomotor processing speed (OR=1.74, 95% CI 1.03 to 2.92). Compared with those without diabetes, those with T1D had lower scores on total cognition, language, executive function/psychomotor processing speed, and verbal episodic memory; they were nearly three times more likely to have low executive function/psychomotor processing speed (OR=2.99, 95% CI 1.66 to 5.437) and nearly two times more likely to have low verbal episodic memory (OR=1.92, 95% CI 1.07 to 3.46). Taken together, these results suggest that the negative effect of diabetes on cognition among older adults is greater in those with T1D than T2D.

The cognitive deficits we report here in older adults with T1D are consistent with prior studies but provide greater detail on specific domains impacted and provide direct comparison with a group of older adults with T2D as well as with a group of older adults without diabetes. The recently published findings from 32 years of follow-up in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study provide important new data on the increasing magnitude of cognitive decline as individuals with T1D enter their late 50s and early 60s.³⁷ They reported significant declines in memory, psychomotor, and mental efficiency as these individuals aged. However, the DCCT/EDIC study does not include a comparison group without diabetes and only includes select cognitive domains that were previously associated with aging and glycemic control. Additionally, a 2005 meta-analysis summarizing the evidence on the effects of T1D on cognitive performance concluded that the evidence strongly supported the hypothesis that T1D was associated with a modest degree of cognitive dysfunction.³⁸ Specific domains in which T1D had significantly lower performance include processing speed, psychomotor

Table 3 Cognitive function in older adults with type 1 diabetes compared with older adults with type 2 diabetes

| | Total cognition | | Language | | Executive function/ psychomotor processing speed | | Verbal episodic memory | | Visual episodic memory | | Simple attention | |
|---|------------------------|-------------------------------|-------------------------------|------------------|--|------------------|---------------------------|-------------------------------|---------------------------|----------------------------|------------------|----------------------|
| | β (95% CI) | β (95% CI) | β (95% CI) | β (95% CI) | β (95% CI) | β (95% CI) | β (95% CI) | β (95% CI) | β (95% CI) | β (95% CI) | β (95% CI) | |
| Model 1: adjusted for race/ethnicity, age, sex, and educational attainment | | | | | | | | | | | | |
| T1D | -0.02 (-0.09 to 0.05) | -0.10 (-0.20 to -0.01) | | | -0.18 (-0.28 to -0.08) | | | -0.17 (-0.29 to -0.04) | | 0.32 (0.21 to 0.43) | | 0.03 (-0.09 to 0.15) |
| T2D | Ref | Ref | | | Ref | | | Ref | | Ref | | Ref |
| Model 2a: model 1 + additional adjustment for stroke, MI, neuropathy, and retinopathy | | | | | | | | | | | | |
| T1D | 0.003 (-0.07 to 0.07) | | -0.09 (-0.19 to 0.01) | | -0.12 (-0.22 to -0.02) | | | -0.18 (-0.31 to -0.05) | | 0.35 (0.23 to 0.46) | | 0.06 (-0.06 to 0.18) |
| T2D | Ref | | Ref | | Ref | | | Ref | | Ref | | Ref |
| Model 2b: model 1 + additional adjustment for depression, PSQI, and BMI | | | | | | | | | | | | |
| T1D | -0.03 (-0.10 to 0.05) | | -0.12 (-0.22 to -0.01) | | -0.20 (-0.31 to -0.09) | | | -0.20 (-0.35 to -0.06) | | 0.33 (0.21 to 0.46) | | 0.05 (-0.09 to 0.18) |
| T2D | Ref | | Ref | | Ref | | | Ref | | Ref | | Ref |
| Model 3: adjustment for all above covariates | | | | | | | | | | | | |
| T1D | -0.002 (-0.08 to 0.08) | | -0.11 (-0.22 to 0.01) | | -0.14 (-0.26 to -0.02) | | | -0.21 (-0.37 to -0.06) | | 0.36 (0.23 to 0.49) | | 0.07 (-0.07 to 0.22) |
| T2D | Ref | | Ref | | Ref | | | Ref | | Ref | | Ref |

Linear regression models comparing cognitive function in those with T1D with those with T2D with varying levels of covariate adjustment. Results in bold are statistically significant.

BMI, body mass index; MI, myocardial infarction; PSQI, Pittsburgh Sleep Quality Index; Ref, reference; T1D, type 1 diabetes; T2D, type 2 diabetes.

Table 4 Association between diabetes type and odds of low cognitive function*

| Cognitive domain | Low cognitive function, n (%) | Comparison of T1D and T2D vs no diabetes | |
|--|-------------------------------|--|---------------------------------------|
| | | OR (95% CI)† | Comparison of T1D vs T2D OR (95% CI)† |
| Total cognition | | | |
| No diabetes | 19 (7.7) | Ref | – |
| T1D | 65 (8.9) | 1.50 (0.84 to 2.67) | 0.95 (0.56 to 1.60) |
| T2D | 25 (10.8) | 1.57 (0.80 to 3.07) | Ref |
| P value | 0.49 | | |
| Language | | | |
| No diabetes | 19 (7.8) | Ref | – |
| T1D | 60 (8.3) | 1.38 (0.77 to 2.47) | 0.95 (0.55 to 1.65) |
| T2D | 23 (10.1) | 1.43 (0.72 to 2.83) | Ref |
| P value | 0.62 | | |
| Executive function/psychomotor processing speed | | | |
| No diabetes | 17 (6.9) | Ref | – |
| T1D | 94 (13.0) | 2.99 (1.66 to 5.37) | 1.74 (1.03 to 2.92) |
| T2D | 24 (10.4) | 1.71 (0.85 to 3.43) | Ref |
| P value | 0.03 | | |
| Verbal episodic memory | | | |
| No diabetes | 17 (7.2) | Ref | – |
| T1D | 74 (10.5) | 1.92 (1.07 to 3.46) | 1.69 (0.94 to 3.06) |
| T2D | 16 (7.5) | 1.11 (0.53 to 2.34) | Ref |
| P value | 0.19 | | |
| Visual episodic memory | | | |
| No diabetes | 21 (8.7) | Ref | – |
| T1D | 36 (5.1) | 0.64 (0.36 to 1.14) | 0.93 (0.49 to 1.79) |
| T2D | 14 (6.1) | 0.69 (0.34 to 1.40) | Ref |
| P value | 0.13 | | |
| Simple attention | | | |
| No diabetes | 21 (8.5) | Ref | – |
| T1D | 55 (7.7) | 0.93 (0.54 to 1.59) | 0.62 (0.38 to 1.02) |
| T2D | 27 (11.8) | 1.47 (0.80 to 2.71) | Ref |
| P value | 0.15 | | |

Results in bold are statistically significant.

*Defined as ≥ 1.5 SD below mean among the no diabetes group.

†Adjusted for age, sex, race, and educational attainment.

Ref, reference; T1D, type 1 diabetes; T2D, type 2 diabetes.

efficiency, attention, cognitive flexibility, and visual perception. Finally, in a comparison of 82 people with T1D (mean age ~65 years) with disease duration >50 years with 30 age-matched people without diabetes, T1D was associated with poorer immediate and delayed recall and psychomotor speed, and a trend toward worse executive function/psychomotor processing speed ($p < 0.05$).³⁹ In prior studies of T2D and cognition, the effect sizes of cross-sectional associations between T2D and cognition have been small to moderate, affecting mainly semantic memory. Consistent with this, we found that although

those with T2D had subtly worse cognitive function than those without diabetes, with the exception of the verbal episodic memory domain, these differences were not statistically significant.

Several factors may account for our findings. Relative to individuals with T2D, people with T1D typically have a much younger age of diabetes onset and remain continuously on insulin from the time of diagnosis. Hence, by the time they reach their mid-60s (the average age in our study), individuals with T1D have managed their disease for decades and likely accumulated decades of exposure

to chronic hyperglycemia.^{40–42} They are also significantly more likely than T2D counterparts to have experienced acute metabolic events^{29 43 44} and may also have a higher burden of microvascular and macrovascular disease.^{45–49} Further, mechanisms underlying T1D differ from those underlying T2D.

We hypothesize that acute metabolic events may be an important factor impacting cognitive function of people with T1D. In our study, among those with T1D, 30% reported a severe hypoglycemic event in the past 12 months and 29% reported a lifetime history DKA; by contrast, among those with T2D, 5% reported past 12-month severe hypoglycemia and <1% reported a lifetime history of DKA. To explore this hypothesis, we conducted a sensitivity analysis excluding individuals with lifetime history of acute metabolic events (hypoglycemic event or DKA). We found that, while our effect estimates did remain statistically significant, there was substantial attenuation of the degree of cognitive deficit observed in the T1D sample, suggesting that acute metabolic events likely play some role in the poorer cognitive function we observe in this group. This finding is supported by our recent reports that severe hypoglycemic events¹¹ and recurrent DKA¹² were associated with poor performance on a number of cognitive domains. It is also supported by results from 32 years of follow-up from the DCCT/EDIC study; this long-term follow-up of 1051 participants (median age 59) provides some of the strongest evidence to date that older adults with T1D experience substantive decline in cognitive function that accelerates with increasing age and is more pronounced in those with more frequent exposure to severe hypoglycemia.³⁷ Another significant contribution was the findings by Chaytor *et al.*²⁵ among a cohort of older adults with T1D (mean age=68.29) that reported increased cognitive impairment among those with two or more severe hypoglycemic events in the past year and among those with one or more microvascular complication. As reported by Chaytor *et al.*²⁵ and others, microvascular and macrovascular disease can also contribute to reduced cognitive function. Prior studies in T1D and in T2D have reported that the presence of microvascular and macrovascular complications contributes independently to worse cognition^{50 51} and faster cognitive decline.^{37 52 53} Although we adjusted for microvascular and macrovascular complications in our models, unmeasured factors related to the higher burden of microvascular and macrovascular complications present with T1D in our sample, such as vascular elasticity and inflammation, may explain some of the poorer cognitive performance we report in this group.

One unanticipated result was the association we found between T1D and better visual episodic memory. Further work is required to explore the reasons underlying the association between T1D and better visual episodic memory.

Strengths of our study include the large sample of older adults with T1D, direct comparison with groups of individuals with T2D and without diabetes, the thorough assessment of cognitive function, including assessment of a range of cognitive domains, and the well-characterized lifetime diabetes history. There are a number of

limitations to consider as well when interpreting our findings. First, 85% of our sample were white and 61% had a college education or higher. While this is a fairly homogenous sample, compared with other studies of adults with T1D,^{18 54–56} 15% non-white participants is relatively diverse. Nonetheless, findings should be replicated in even more diverse samples. The incidence of T1D is increasing most sharply in minority populations and ensuring these populations are represented is essential. Additionally, older adults with T2D are increasingly recognized as a heterogeneous group. Our sample includes a relatively small sample of participants with T2D and these participants were selected to serve as matched controls to the T2D sample; as such, this subset of individuals with T2D may not reflect the broader population of older adults with T2D. In addition to these limitations with the study sampling, our study relied on self-reported medical history, which may introduce recall bias into our estimates. In the present study, we did not have access to hemoglobin A1c (HbA1c) laboratory data, a measure which has been previously shown to be associated with risk of dementia in older adults with T1D and T2D. Given our inability to adjust for HbA1c, it is possible that part of the observed differences in cognitive function by diabetes type may actually be explained by differences in glycemic control. We also did not assess blood pressure. Additionally, while we were able to characterize lifetime history of a number of diabetes-related characteristics (eg, age of onset, exposure to hypoglycemia, DKA), our study did not collect data on exposure to hyperosmolar hyperglycemic syndrome (HHS). In T1D, DKA is the primary form of hyperglycemic crisis, but in T2D DKA is relatively rare, while HHS, another type of hyperglycemic crisis, is much more common. Our models did not include information on HHS exposure. Finally, in the current study we do not have any neuroimaging data and thus cannot examine biomarkers of vascular brain injury or neurodegeneration to understand how this may contribute to differences in cognition.

In summary, in this study of older adults, we found significantly poorer cognitive function in those with T1D as compared with those with T2D and as compared with those without diabetes. This association was robust to varying levels of confounder adjustment. A modest degree of cognitive deficit was observed in those with T2D as compared with those without diabetes, but this association was less pronounced than the deficit observed in T1D and did not remain statistically significant after adjustment for confounders and mediators. Our findings underscore the importance of close monitoring of cognitive function in older adults with T1D as they enter older adulthood. Future studies should delineate how to reduce risk for this vulnerable population who are newly surviving to old age.

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Supplementary Table 1. Sample characteristics of those who completed and did not complete all cognitive tests.

| | | Overall (N=1,213) | Excluded (n=93) |
|--|---------------------------------|----------------------|--------------------|
| Demographics | | | |
| Age (years) Mean (SD) | | 67.79 (6.60) | 70.40 (7.18) |
| Female, n (%) | | 621 (51.20) | 34 (48.57) |
| Race/ethnicity, n (%) | | | |
| | White | 1026 (84.58) | 60 (85.71) |
| | Hispanic | 21 (1.73) | 5 (7.14) |
| | Asian | 21 (1.73) | 1 (1.43) |
| | African American | 97 (8.00) | 1 (1.43) |
| | Other | 44 (3.63) | 2 (2.86) |
| | Unknown | 4 (0.33) | 1 (1.43) |
| Highest level of educational attainment, n (%) | | | |
| | Some college or less | 473 (38.99) | 31 (44.29) |
| | Bachelor's degree | 371 (30.59) | 18 (25.71) |
| | Graduate or professional degree | 365 (30.09) | 19 (27.14) |
| Diabetes | | | |
| | T1D | 734 (60.51) | 43 (61.43) |
| | T2D | 232 (19.13) | 16 (22.86) |
| | No diabetes | 247 (20.36) | 11 (15.71) |
| Geriatric Depression Scale, mean (SD) | | 29.08 (6.33) | 3.52 (3.73) |
| Pittsburg Sleep Quality Index, mean (SD) | | 1.99 (2.27) | 8.59 (3.15) |
| Stroke, n (%) | | 8.02 (2.72) | 11 (15.71) |
| Myocardial Infarction, n (%) | | 99 (80.06) | 10 (14.29) |
| Retinopathy, n (%) | | 122 (10.06) | 23 (32.86) |
| Nephropathy, n (%) | | 56 (4.62) | 7 (10.00) |
| Neuropathy, n (%) | | 333 (27.45) | 30 (42.86) |
| Age at diabetes diagnosis, mean (SD) | | 34.68 (18.49) | 30.90 (16.83) |
| Diabetes duration in years, mean (SD) | | 32.93 (17.85) | 38.81 (16.73) |
| Severe hypoglycemia, n (%)* | | 246 (25.47) | 18 (25.71) |
| Diabetic ketoacidosis, n (%)** | | 207 (21.43) | 16 (22.86) |

Supplemental Table 2. Association between cognitive function and diabetes type among those with no prior history of DKA or severe hypoglycemia

| | Global cognition β (95% CI) | Language β (95% CI) | Executive function β (95% CI) | Verbal episodic memory β (95% CI) | Visual episodic memory β (95% CI) | Simple attention β (95% CI) |
|-------------|--------------------------------|-----------------------------|----------------------------------|---|---|-----------------------------------|
| No diabetes | Ref | Ref | Ref | Ref | Ref | Ref |
| T1D | -0.04 (-0.12, 0.05) | -0.14 (-0.26, -0.03) | -0.14 (-0.26, -0.03) | -0.05 (-0.20, 0.11) | 0.19 (0.05, 0.32) | -0.03 (-0.18, 0.13) |
| T2D | -0.06 (-0.15, 0.03) | -0.06 (-0.18, 0.06) | -0.07 (-0.19, 0.06) | 0.09 (-0.07, 0.25) | -0.18 (-0.32, -0.04) | -0.05 (-0.21, 0.10) |

*Supplemental Table 2 Footnotes – Sample for this sensitivity analysis includes individuals with no prior history of DKA or severe hypoglycemia and is as follows for the three diabetes groups: no diabetes, n=247; T1D, n=371; T2D, n=219. Models are adjusted for race, age, sex, education, depression, sleep quality, BMI, stroke, MI, nephropathy, retinopathy, and neuropathy.