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BACKGROUND. We aimed to characterize factors associated with the under-studied complication of cognitive decline in aging people with long-duration type 1 diabetes (T1D).

METHODS. Joslin "Medalists" (n = 222; T1D ≥ 50 years) underwent cognitive testing. Medalists (n = 52) and age-matched non-diabetic controls (n = 20) underwent neuro- and retinal imaging. Brain pathology (n = 26) was examined. Relationships amongst clinical, cognitive and neuroimaging parameters were evaluated.

RESULTS. Compared to controls, Medalists had worse psychomotor function and recall, which associated with female gender, lower visual acuity, reduced physical activity, longer diabetes duration and higher inflammatory cytokines. On neuroimaging, compared to controls, Medalists had significantly lower total and regional brain volumes, equivalent to 9 years of accelerated aging, but small vessel disease markers did not differ. Reduced brain volumes associated with female sex, reduced psychomotor function, worse visual acuity, longer diabetes duration and higher inflammation, but not with glycemic control. Worse cognitive function, lower brain volumes, and diabetic retinopathy correlated with thinning of the outer retinal nuclear layer. Worse baseline visual acuity associated with declining psychomotor function in longitudinal analysis. Brain volume mediated the association between visual acuity and psychomotor function by 57%. Brain pathologies showed decreased volumes, but predominantly mild vascular or Alzheimer's-related pathology.

CONCLUSION. This first comprehensive study of cognitive function, neuroimaging and pathology in aging T1D individuals […]

Characterization of cognitive decline in long-duration type 1 diabetes by cognitive, neuroimaging and pathological examinations

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ABSTRACT

Background

We aimed to characterize factors associated with the under-studied complication of cognitive decline in aging people with long-duration type 1 diabetes (T1D).

Methods

Joslin "Medalists" (n=222; T1D≥50 years) underwent cognitive testing. Medalists (n=52) and age-matched non-diabetic controls (n=20) underwent neuro- and retinal imaging. Brain pathology (n=26) was examined. Relationships amongst clinical, cognitive and neuroimaging parameters were evaluated.

Results

Compared to controls, Medalists had worse psychomotor function and recall, which associated with female gender, lower visual acuity, reduced physical activity, longer diabetes duration and higher inflammatory cytokines. On neuroimaging, compared to controls, Medalists had significantly lower total and regional brain volumes, equivalent to 9 years of accelerated aging, but small vessel disease markers did not differ. Reduced brain volumes associated with female sex, reduced psychomotor function, worse visual acuity, longer diabetes duration and higher inflammation, but not with glycemic control. Worse cognitive function, lower brain volumes, and diabetic retinopathy correlated with thinning of the outer retinal nuclear layer. Worse baseline visual acuity associated with declining psychomotor function in longitudinal analysis. Brain volume mediated the association between visual acuity and psychomotor function by 57%. Brain pathologies showed decreased volumes, but predominantly mild vascular or Alzheimer's-related pathology.

Conclusion

This first comprehensive study of cognitive function, neuroimaging and pathology in aging T1D individuals demonstrated that cognitive decline was related to parenchymal rather than neurovascular abnormalities, unlike type 2 diabetes, suggestive of accelerated aging in T1D. Improving visual acuity could perhaps be an important preventive measure against cognitive decline in people with T1D.

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INTRODUCTION

Both Type 1 (T1D) and Type 2 (T2D) diabetes are rapidly increasing in prevalence globally and affect more than 33 million people in the U.S, including 25% of the aging population (people >65 years) (1). Along with other major complications, cognitive dysfunction is now recognized as a major morbidity associated with diabetes, and poses great socioeconomic burdens and reduced quality of life (2-5). Diabetes-associated cognitive decline may have multiple underlying mechanisms, including vascular abnormalities, and changes in glucose, insulin sensitivity and amyloid metabolism (2, 3). Studies examining diabetes-associated cognitive dysfunction have mostly focused on T2D, which itself, along with insulin resistance and obesity, are significant risk factors for dementia especially in Alzheimer's and related disorders (6). Detailed clinical characterization of cognitive dysfunction in a large cohort with long T1D duration has been limited given that living longer than 55 years among those with T1D has only become possible recently (7, 8). Studies in younger T1D populations have suggested the important roles of poor glycemic control and hypoglycemia on cognitive decline, but their role in older T1D populations remains undefined. (2, 3, 9, 10). Additionally, modifiable risk factors for T1D-associated cognitive decline may differ in older age groups compared to younger people (11). Brain imaging studies in T1D have been restricted to younger to mid-life adults, with reports of vascular and parenchymal changes (12). However, it is not clear whether these changes can be extrapolated to older individuals with long standing T1D (12). No studies have comprehensively characterized both neuroimaging and pathological brain examinations and their relationships to cognitive changes in T1D. Furthermore, as retinal neurodegeneration is an early event in the pathogenesis of diabetic retinopathy and could run in parallel with brain neurodegeneration (13-17), it is important to further tease out these relationships in the context of T1D.

The Joslin 50-year Medalist Study ("Medalists"), a cohort of individuals with 50+ years of T1D, is exceptionally well-suited to characterize and identify potential novel markers of cognitive decline, especially since they do not exhibit clinical signs of insulin resistance and have relatively good glycemic and metabolic control (18-23). Yet, as reported, Medalists had similar levels of cognitive impairment as age-matched individuals with type 2 diabetes (T2D) and greater levels of impairment compared to age-matched individuals without diabetes (24). Thus, we aimed to characterize factors associated with cognitive decline in this elderly cohort with very long duration of T1D in a first comprehensive study of cognitive and clinical assessments, retinal and brain imaging, gross and histopathological examination of post-mortem brain specimens.

RESULTS

Baseline characteristics of study groups

Supplementary Table 1 summarizes the baseline characteristics of Medalists in the overall cohort (n=1034), and the following subsets: cognitive (n=222), brain imaging (n=52), longitudinal (n=48) and brain donors (n=26). At baseline, Medalists were 55% female, mean age 66 years, with 53 years of T1D, mean glycated hemoglobin (HbA1c) of 7.2%, and body mass index (BMI) of 26 kg/m^2. While 77% of Medalists reported a history of hypertension, the average systolic and diastolic blood pressures were very well-controlled, coupled with a cardiac-favorable lipid profile (mean LDL-c of 81 mg/dL and HDL-c of 65 mg/dL) and mean estimated glomerular filtration rate (eGFR) of 69.7 ml/min/1.73 m^2, normal for the age group. About 80% of Medalists reported that they do exercise. A third of Medalists had proliferative retinopathy (PDR), 40% had reported cardiovascular disease (CVD), but only 12% had diabetic nephropathy (DN). Participants of the various subsets were fairly representative of the overall study population, except for the brain imaging group which had a smaller proportion of individuals with CVD (19% vs. 40%) and DN (2% vs. 13%) at baseline. Only 17% had at least one APOE risk allele as compared to 26% in the overall study. The brain donor group had a higher proportion of individuals with CVD (46%) and DN (15%) at baseline than the overall Medalist cohort (Supplementary Table 1).

Cross-sectional characteristics of the study participants at time of cognitive or neuroimaging study visit, or last visit for brain donors, are shown in Table 1. Mean age at the time of the cognitive study was 71 years and duration of diabetes 61 years. Other characteristics are comparable to the baseline study visit. In the neuroimaging study group there were about 50% females and an average age at study visit of 72 years, with higher HbA1c as expected, although

still very good glycemic control, and a better lipid profile compared to age-matched non-diabetic controls (Table 1). At time of brain MRI, the proportion of those with self-reported hypertension was 72% for Medalists and 47% for controls, while CVD was reported for 35% of the Medalists as compared to only 22% among control subjects (Table 1). There were no significant differences between Medalists and controls with respect to sex, age, BMI (both were in the non-overweight range), renal function, education or lifestyle.

Cognitive function

Compared to controls, Medalists had significantly worse recall, psychomotor function, and global cognition (Table 1). In bivariate analysis among Medalists, worse psychomotor function in both dominant and non-dominant domains was ($p<0.05$) associated with increased age, longer duration of diabetes, increased Interleukin-6 (IL6), worse renal function (higher albumin-creatinine ratio [ACR] and lower eGFR), and lower visual acuity. Better function was associated with higher education (Figure 1). Worse motor function in the dominant hand also associated significantly with higher C-reactive protein (CRP) and PDR. In the non-dominant hand it was associated with higher systolic blood pressure, IL1β and coronary artery calcification (CAC) (Figure 1). In multivariable models incorporating all these significant covariates, only education, duration, and visual acuity remained significant ($p<0.05$) for both dominant and non-dominant hands, while IL6 remained significant for the dominant hand (Supplementary Table 2).

Worse immediate recall was associated ($p<0.05$) with higher triglyceride-HDL ratio, CVD and CAC. Better immediate recall was associated with female sex, higher HDL and total cholesterol, and better insulin sensitivity (Figure 1). Better delayed recall ($p<0.05$) was associated with female sex, CRP and Interferon-γ (IFNγ) levels, while worse delayed recall was associated with IL1β (Figure 1). In multivariable models, female sex remained significant for both types of

recall, while IL1β and IFNγ also remained significant for delayed recall (Supplementary Table 2). Worse executive function associated significantly with higher age, duration, LDL, ACR, triglycerides, total cholesterol, IL1β, CAC and with lower visual acuity (Figure 1). In multivariable models, total cholesterol and IL1β remained significant for associations with executive function (Supplementary Table 2). Better working memory was associated significantly with higher education and estimated insulin sensitivity index (eIS), while worse working memory was associated with higher triglycerides, triglyceride-HDL ratio, visceral adiposity index (VAI) and CVD (Figure 1). However, none of these remained significant in multivariable analysis (Supplementary Table 2). None of the cognitive domains were associated with HbA1c, lifetime hypoglycemia severity, continuous glucose monitoring (CGM) indices, or advanced glycation end products (AGEs), including carboxymethyl-lysine (CML), carboxyethyl-lysine (CEL), and methylglyoxal-hydroimidazolone-1 (MGH1) (Figure 1B).

Better global cognition delayed recall (captured by memory index score [mis]) was associated with female sex and CML, while worse outcome was associated with age at diagnosis, SBP and eGFR. Worse total global cognition was associated with increasing age, SBP, and CAC, and with reduced visual acuity. However, in multivariable models, female sex, SBP and eGFR remained significant for the global cognition recall, while visual acuity remained significant for the total global cognition (Supplementary Table 2).

For physical activity reported in the Paffenbarger surveys, in age, sex and education adjusted models, increased number of daily stairs climbed and blocks walked were associated with better executive function and psychomotor speed, respectively, ($p<0.05$) (Supplementary Table 3). Increased weekly duration of and caloric expenditure from swimming associated with better delayed recall (Supplementary Table 3).

From the lifestyle activity questionnaire (LAQ), driving was associated with better executive function (Supplementary Table 3). Sewing and talking about politics reduced psychomotor function, while going to the movies was associated with poorer executive function (Supplementary Table 3).

Higher adherence to Mediterranean, Dietary Approaches to Stop Hypertension (DASH) and Empirical Index for Hyperinsulinemia (EDIH) diets were associated with better working memory (Supplementary Table 4). The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet was not significantly associated with any of the cognitive domains. Higher anti-inflammatory score for the Empirical Dietary Inflammatory Pattern (EDIP) index was associated with worse executive function (Supplementary Table 4).

Structural volumetrics

Compared to non-diabetic individuals, Medalists had significantly ($p<0.05$) lower volumes in regions of the total brain, total gray matter, total white matter, occipital lobe, and deep gray matter – which is the subcortical region comprising the basal ganglia and the thalamus; and a marked but non-significant ($p=0.08$) lower volume in the Alzheimer's disease signature region, comprised of hippocampal, parahippocampal, entorhinal and related areas (Figure 2A-B). These volume reductions translated to Medalists' brains being about 8-13 years older than those of non-diabetic individuals (Figure 2A-B).

In models adjusted for intracranial volume, lower volumes across all brain regions examined in the T1D Medalists was associated with worse motor function (Figure 2C). Nominal associations were observed between better executive function and higher total brain, total white matter and hippocampal volumes, while immediate recall associated with occipital lobe volume (Figure 2C).

In models additionally adjusted for age, sex and education, these associations remained significant ($p<0.05$), except the following: motor function (both D and ND) with total white matter and frontal lobe volumes, immediate recall and motor function (D) with occipital lobe volume, motor (ND) with frontal lobe volume and motor (D) with deep gray matter volume (Supplementary Table 5).

In control subjects, none of the above associations between cognitive function and brain volumes were observed, except motor function of the dominant side which was associated with reduced total white matter volume (Figure 2D).

In Medalists, education, exercise and waist-hip ratio associated with higher volumes in most regions, while female sex, increasing age, diabetes duration, HDL, total cholesterol and IL1β and lower visual acuity associated with lower brain volumes (Figure 3). A higher BMI and lower TNFα also associated with a higher volume of the Alzheimer disease signature region. PDR was associated with decreased frontal lobe volume (Figure 3). Lifetime hypoglycemic severity was associated with lower deep gray matter volume. In multivariable models accounting for all significant associations for each region, sex remained significant for all volumes except parietal lobe (Supplementary Table 6). Additionally, visual acuity remained significant for associations with Alzheimer disease signature region, temporal lobe, total brain, and total white and gray matter volumes. IL1β remained significant for associations with total brain, total white and gray volumes, hippocampal and Alzheimer disease signature regions (Supplementary Table 6). Duration remained significant for total brain, total white matter and Alzheimer disease signature region. For the latter region, HDL and TNFα also remained significant. Education also remained significant for frontal lobe volume, age remained significant for occipital lobe volume, and

lifetime hypoglycemic severity for deep gray matter region. For parietal lobe volume, only ACR remained significant (Supplementary Table 6).

There were no associations between brain volumes and age at diagnosis, HbA1c, CGM indices, or advanced glycation end products (Figure 3B). Lifetime hypoglycemic severity was associated ($p<0.05$) with lower volume of the deep gray matter region, but not with other volumes (Figure 3B). Other markers of inflammation or insulin resistance did not correlate with volumes (Figure 3C-D). Except for PDR, no associations were observed with diabetic vascular complications (Figure 3E).

Vascular imaging

No significant differences were observed between Medalists and controls in the number of microbleeds, volume of white matter hyperintensities (WMH) or number of lacunar infarcts (Figure 4A-C), nor were any differences observed in cerebral perfusion rates (Figure 4D).

WMHs did not associate with cognitive function in the Medalists (Supplementary Figure 1A). Better motor function of the non-dominant side was associated with higher occipital lobe perfusion, while worse global cognition associated with higher perfusion of the deep gray matter region (Supplementary Figure 2A). In control subjects, higher cerebral perfusion in all regions was associated with worse executive function (Supplementary Figure 2B).

Increased WMHs were associated with worse renal function and higher coronary artery calcification scores (Supplementary Figure 1B-C). Cerebral perfusion improved with Females, higher HDL, HbA1c, ACR and insulin sensitivity, and with lower BMI, DBP, waist-hip ratio, LDL, cholesterol and CRP (Supplementary Figure 2C). In multivariable models, mainly BMI and sex remained significant. ACR remained significant for temporal lobe and hippocampus.

LDL was significant for hippocampus and Alzheimer's disease signature region. CRP in addition to age and sex remained associated with deep gray matter perfusion (Supplementary Figure 2C). There were no associations seen between WMHs or cerebral perfusion with other complications (CVD, PDR, DN, neuropathy), markers of insulin resistance, vascular markers, hypoglycemia or CGM parameters or AGEs.

Histopathology

Characteristics of brain donors at their last visit are shown in Table 1, and summary of their brain histopathology are shown in Figure 5, Table 2 and Supplementary Table 7. About 42% of the brain donors died due to CVD, 11% due to renal failure and 8% due to Alzheimer's disease (Figure 5A). The average brain weight was 1173g (±133g), and females' brains (n=7) were on average 120.3 ± 54.5 g lighter than male brains (p=0.037) (Figure 5B). Medalists' average brain weights for both males and females were significantly ($p<0.0001$) lower than those in comparative age groups (66+ years) in a referenced normal aging population (25) (Figure 5C). Brain volumes were mildly reduced (Figure 5D). Vascular pathology (infarcts, bleeding, and atherosclerosis) was mostly mild (Figure 5D-E) as per standard guidelines (26, 27). As expected in this older age group, there was evidence of Alzheimer's-related deposits, as per Braak staging (28), such that 8 % had no deposits, 46 % had Braak stage I-II involvement, 38 % had stage III-IV involvement, 8 % had stage IV-V involvement (Figure 5D-E).

Among three of the five brain donors who had previous cognitive assessments, cognitive scores deviated by 1.5 S.D. of the means of those without diabetes. Despite poor cognitive scores, two of these individuals had only Braak stage I Alzheimer's pathology, and one had Braak III-IV along with neocortical Lewy body pathology (Table 2). Of the two patients who had been

diagnosed with Alzheimer's disease, one had Braak stage I-II and the other had stage V (Table 2). The patient that had two APOE risk alleles had Braak stage IV pathology (Table 2).

Retinal imaging

Since visual acuity and PDR consistently correlated with various parameters of cognitive dysfunction and brain volumetric losses, we evaluated detailed changes in retinal layers in relation to these brain parameters. Increased thickness of the retinal outer nuclear layer (ONL), composed primarily of photoreceptors, was significantly associated with higher brain volumes in all regions except the deep gray matter, hippocampus and temporal lobe (Figure 6A). Other retinal layers did not associate with brain volumes (Supplementary Figure 3). Mediation analysis showed that total brain volume mediated 57 % of the association between visual acuity and psychomotor function (Figure 6B), and 73 % of the association between ONL thickness and psychomotor function (Figure 6C).

Longitudinal study

A subset of Medalists (n=48) had 2 or more cognitive visits with an average follow-up time of 4.8 years between visits (Table 1 and Supplementary Table 1). Declines observed in recall and psychomotor cognitive domains (Supplementary Table 8), although none were significant. A strong association was observed between lower visual acuity at first cognitive visit and reduced psychomotor function in the non-dominant side over time, independent of age, sex or duration of T1D (Supplementary Table 8).

DISCUSSION

In this first comprehensive study of clinical and cognitive testing, retinal and neuroimaging, and brain gross and histopathology exams, we show that aging individuals with long-duration of T1D, despite excellent glycemic and cardiometabolic profiles, have worse cognitive function compared to people without diabetes, and that this is related mainly to brain parenchymal loss and less to vascular or Alzheimer's-related phenomena, unlike findings in T2D (29, 30).

Cognitive studies in aging populations with T1D have been sparse. Several studies, including ours, have reported cognitive decline in domains affecting recall and psychomotor function (7, 24, 31, 32). Lack of associations with hypoglycemia and cognitive function or brain structure in our study are consistent with previous reports in prospective studies including the DCCT and the Stockholm Diabetes Intervention Study (33, 34). However, unlike previous reports (9, 31, 34), our study did not observe an association between hyperglycemia and cognitive function. Perhaps this lack of association between HbA1c and cognitive function or brain structure may be due to Medalists' tight glycemic control and little variability in HbA1c. This is unlikely though, as other short- and long-term measures of glycemic control including CGM metrics, or AGEs in our study did not associate significantly with cognitive decline. Moreover, intensive glycemic control in the DCCT & Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial have not shown benefit for cognitive function (35, 36). Nonetheless, despite long duration of excellent glycemic, lipid and blood pressure control, Medalists still exhibit significant cognitive decline and lower brain volumes compared to people without diabetes, pointing to yet uncovered T1D-related factors that may play a role in their cognitive decline.

The results of brain imaging and pathological exams in this study differ from those observed in individuals with T2D. While global atrophy is also a feature commonly seen in T2D, the volume

reduction is generally modest, comparable with 3-5 years of normal aging (12, 29), while we are observing 9 years of accelerated global atrophy in T1D compared to normal aging individuals. Furthermore, regional volume loss in T2D predominantly affects memory areas like the hippocampal regions or temporal lobe (37), while we observed atrophy predominantly in the occipital lobe and subcortical regions of the basal ganglia and thalamus. Additionally, small vessel disease has been commonly and consistently reported in T2D, including WMHs and lacunar infarcts on MRI and histopathology (29, 30), whereas our findings did not show significant increases in small vessel disease in T1D Medalists compared to non-diabetic controls, which were confirmed by minimal vascular pathology in post-mortem brain examinations.

In T2D, while more than 40% of people have moderate-to-severe Alzheimer's related pathology in brain autopsies, multiple etiologies have been suggested for cognitive decline including vascular and cerebral insulin resistance, inflammation or endothelial dysfunction due to accumulation of AGEs or toxic lipids or proteins in the vasculature (38-41). For the Medalists with chronic T1D, Alzheimer's-related immunostaining, including amyloid plaques and Braak staging of tau, showed pre-dominantly mild-to-moderate pathology, even in the three individuals who had poor cognitive function, the one individual with two APOE risk alleles, and one of the patients whose reported cause of death was Alzheimer's disease. In the other patient who had a clinical Alzheimer's diagnosis, Braak V staging was seen with frequent amyloid plaques. One of the patients with poor cognitive function also had cortical Lewy body pathology along with Braak stage III-IV, suggestive of a mixed picture underlying their cognitive decline. Medalists also exhibited very well-controlled cardiometabolic profiles and insulin resistance markers were not associated with cognitive or neuroimaging outcomes, again suggesting that underlying mechanisms and pathologies of cognitive decline in T1D may differ from T2D. However, some

inflammatory cytokines including IL1β and IL6 did associate with cognitive decline and lower brain volumes in our study, suggesting that the role of inflammation needs to be investigated.

Recently, neuroimaging studies by the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) in participants with a mean age of 59 years, and on average 38 years of T1D (31, 42) reported reductions in total brain, white and gray matter volumes, the latter being associated with poor cognitive function, while they reported no markers of Alzheimer's-related neurodegeneration (31). However, their reports lacked pathological confirmation (42). Our study is the first to examine an aging population with mean age of 72 years and 50+ years of T1D, where post-mortem brain exams provided the strongest evidence alongside MRI changes that underlying pathologies of cognitive decline in aging individuals with long-duration T1D are probably unrelated to vascular or Alzheimer's dementia, differing from T2D (29, 30).

Despite a low prevalence of nephropathy and excellent glycemic control without dyslipidemia, obesity or insulin resistance, Medalists still exhibited significant cognitive decline with corresponding brain atrophy. Thus, it is important to identify potential factors that may mediate these effects. Female gender significantly associated with better cognitive function but lower brain volumes, consistent with previous reports in the general population and in people with diabetes where women perform better in cognitive tests than men (43-45), yet have a greater risk of dementia (46-48). Perhaps this is because women live longer than men, or perhaps their higher cognitive reserves during testing mask underlying functional aberrations, thus they only get diagnosed at more advanced stages (45, 46). Our study supports this hypothesis, given the lower brain volumes observed in women despite better cognitive function. Female hormones have been

suggested to play a protective role on brain health but our study population includes mostly menopausal women given the age of the participants.

Diet and physical activity are known protective factors against cognitive decline (49), and our study supports their protective roles even in an elderly population with long-duration T1D and good cardiometabolic control. Specifically, the Mediterranean and DASH diets, with high contents of fresh fruits and vegetables and low amounts of processed meats, seem to have beneficial effects for working memory. Increased physical activity like number of stairs climbed or blocks walked daily were associated with better executive and psychomotor function, respectively, while swimming benefitted delayed recall.

An interesting finding in this study that has not been discussed in any of the cognitive studies involving T1D or T2D populations was the association of worse visual acuity with both worse cognitive function and lower brain volumes even after multivariable adjustments. These findings support our previous report showing associations between retinal ONL thickness and psychomotor function as well as severity of PDR (13). Indeed, the retina is a "window" to the brain due to shared embryonic origins, and as retinal neurodegeneration is an early event in the pathogenesis of DR, these could run parallel with brain neurodegeneration (13-17). While it is not surprising that loss of visual acuity will adversely affect psychomotor function during clinical testing, the significant association of both visual acuity and selective ONL thinning with brain volumes, strongly indicated that there are biological interactions amongst these factors. Severity of PDR correlated to almost all retinal layers, yet psychomotor function and immediate recall were particularly affected by thinning of the ONL, which is composed mainly of photoreceptors, rods and cones (13). In addition, our results showed that total brain volume mediated 57% and 73% of the associations between psychomotor function and visual acuity or

ONL thickness, respectively. Since severity of PDR is associated with changes in many retinal layers, the selective finding of only ONL thinning being associated with worse visual acuity and lower brain volumes supports the novel concept that visual acuity may have an independent effect on T1D-related cognitive decline. This is unlike Alzheimer's and related disorders, where all retinal fiber layers and even retinal blood flow are affected (50). While pre-clinical studies in animals suggest that there is photoreceptor death in diabetes, this, however, has not been widely reported in human studies and warrants more investigations (51). It is possible that the reduction of mental stimulation resulting from poor visual acuity results in worse psychomotor function and its associated reduction of certain total and regional brain volumes (the sensory loss consequence theory) (52). This is supported by the longitudinal sub-study, where visual impairment assessed at time of first cognitive visit was associated with further psychomotor function decline after 3-5 years of follow-up. Another possibility is that both visual impairment and cognitive decline have a common underlying mechanism, such as inflammation or neurodegeneration (53). As long-term exposure to hyperglycemia can lead to neuroinflammation in both the brain and retina, cognitive decline may be attributed to this common process rather than to the sensory loss theory. Nonetheless, it is also possible that this latter effect could contribute to worsening the progression of cognitive decline. Associations between visual acuity and cognitive functioning have been suggested in non-diabetic populations such as the Salisbury Eye Evaluation Study (54) and the Age-Related Eye Disease Study (55) among others (52, 56), but have remained undiscussed for diabetes. Thus, our findings suggest the interesting possibility that rigorously targeting improvements in visual acuity may be a crucial approach to primary and secondary prevention of cognitive decline in aging populations with T1D. The optimal timing and required nature of these interactions remains to be determined.

Our study has several strengths, including access to a well-characterized and richly-phenotyped elderly population with long-duration T1D; detailed and high-quality cognitive, retinal and neuroimaging assessments; all study participants including cases and controls underwent neuroimaging on the same MRI machine under the same protocol; availability of brain specimens and high-quality gross and histopathological examinations; and the opportunity to examine multiple modifiable risk factors beyond poor cardiometabolic profiles that are known to associate with cognitive decline.

Our study has certain limitations. This was a cross-sectional study with limited power and a small group of non-diabetic controls. However, we still observed relatively strong associations with our main findings and the additional longitudinal component lends a directionality to our hypothesis. Second, all of the 26 brain donors, except five, did not have cognitive or brain MRI data to make direct correlations. However, the four individuals that had poor cognitive function and brain pathology only exhibited minimal Alzheimer's and vascular pathology, thus supporting the MRI findings. Third, we were unable to make any inferences about MCI or dementia-related outcomes as the majority of the Medalists were cognitively intact. Perhaps Medalists are experiencing subtle diabetes-related cognitive decrements greater than controls but these are not impairing them functionally. Fourth, we did not assess more definitive Alzheimer's related biochemical or imaging markers including PET scans or collection of cerebrospinal fluid for amyloid or tau assessment. Last, as the Medalists are a unique group of individuals with T1D having good cardiometabolic control, the lack of neurovascular contributions to their cognitive decline may not necessarily be generalizable to other populations with T1D and studies need to be conducted in aging non-Medalists. Future studies would also need to include a spectrum of

cognitive functioning and imaging studies including PET in a large-scale longitudinal follow-up research design, as well as brain pathological studies.

In conclusion, this is the first comprehensive study of cognitive, brain imaging and pathology in people with long-duration T1D and excellent cardiometabolic profiles. We have provided strong evidence that cognitive decline in T1D is associated with lower brain volumes but not vascular or Alzheimer's related pathologies. In addition, besides changes in diet and activity levels, targeting visual acuity improvements and retinopathy severity may be crucial to preventing cognitive impairment in these individuals.

METHODS

Sex as a biological variable

This study recruited both males and females in equal proportions. Sex as a biological variable is considered for all analyses.

Study Population

The Joslin 50-year Medalist Study ("Medalists") is a well-characterized cohort of individuals (n=1,033) recruited from across the U.S. with well-documented T1D for ≥50 years, as previously described (18-23). The study population consists of 50 % females, 94 % non-Hispanic Whites, 1.6% American Indian or Alaska Native, 0.45 % non-Hispanic Blacks, 0.9 % Hispanic, and 3 % unreported ethnicity. They have been actively followed up and richly phenotyped at the Joslin Diabetes Center via comprehensive clinical exams, food frequency and exercise questionnaires, ophthalmic, renal and cardiac exams, including imaging, general hematological and clinical chemistry studies, and mixed-meal tolerance studies. All patients undergo HLA typing and autoimmune markers, HbA1c, CRP, lipid and renal profiling, and C-peptide measurements. The bio-bank contains plasma, serum and mononuclear cells from all participants, and post-mortem organs (eyes, kidneys, pancreas, heart and brains) from a subset (18-23).

Thus far, 222 Medalists have undergone clinical cognitive testing, as well, 52 of these Medalist participants and 20 age-matched controls underwent additional brain imaging studies. The study was open to all 50-Year Medalist Study participants who previously indicated willingness to be contacted regarding participation in further studies. Participants were included in the brain imaging studies if they did not have contraindications to MRI. A subset of Medalists (n=48) who had at least 2 cognitive study visits formed part of the longitudinal sub-study. Brain donors

(n=26) were Medalists who had previously consented for organ donation and from whom brains were procured for pathological exams. Of these brain donors, 5 individuals had previous cognitive testing. A flowchart of the study design is outlined in Supplementary Figure 4.

Comprehensive clinical assessment: Clinical and cognitive assessments done in the Medalist study have been described previously (13, 18-24). Briefly, the following measures were administered by trained staff at the study visit. General: Updated medical history, complications, vitals, cardiometabolic assessments and clinical labs as per standard protocols by Quest Diagnostics (Seacaucus, NJ). Cognition: The cognitive battery included the following reliable, previously described measures (57): The Montreal Cognitive Assessment (MOCA, for global cognition) (58); The Wechsler Abbreviated Scale of Intelligence III (IQ); The Wechsler Memory Scale III (working memory); The Rey Auditory Verbal Learning Test (RAVLT, for immediate and delayed recall); The Delis-Kaplan Executive Function System (executive function); The Grooved Pegboard (psychomotor speed and efficiency) (57). Standardized t-scores were calculated for the memory domains, with increasing scores representing better cognition. Higher scores for motor domains represented worse times to complete the pegboard test. Participants were screened for possible mild cognitive impairment (MCI) based on the following criteria: A cut-off value of <26 out of 30 points on the MOCA or <35 points on the RAVLT immediate or delayed recall tests (59). APOE4 genotypes: were extracted from the existing Medalists' genomic database using tools such as PLINK 1.9 (Purcell, MA) and GTOOL (Freeman, UK). Physical Activity and lifestyle: Physical activity was captured by Paffenbarger questionnaires (60), while lifestyle via Lifestyle Activity Questionnaires (LAQ) (61). Diet was captured using validated food frequency questionnaires (62, 63), and adherence to the following dietary patterns were derived as previously described, including, alternate Mediterranean (aMed) (64), Dietary

Approaches to Stop Hypertension (DASH) (65), Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) (66, 67), Empirical Index for Hyperinsulinemia (EDIH) and Empirical Dietary Inflammatory Pattern (EDIP) (68).

Cardiac assessments: CVD was captured by self-reported occurrence of coronary artery disease, myocardial infarction, angina, cardiac or leg angioplasty, or coronary bypass graft surgery. Coronary artery calcification (CAC) CT-scans were obtained using a 320 detector-row system (Aquilion ONE, Toshiba Medical Systems, Japan) and scored using prospective ECG gating without contrast. Agatston scores were derived by radiologists at Brigham and Women's Hospital, Boston, MA, USA.

Renal assessments: Serum creatinine and urine albumin-creatinine ratios were measured via standard methods at Quest Diagnostics (Seacaucus, NJ). Serum creatinine-based estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration algorithm (69), and DN was defined using a cut-off eGFR < 45 ml/min/1.73 m^2.

Markers of insulin resistance: The waist-hip ratio was calculated with waist circumference measured at the midpoint between the iliac crest and the lower rib margin, while hip circumference measured at the maximum circumference around the buttocks posteriorly and pubic symphysis anteriorly. Surrogate measures of insulin resistance were also evaluated using the estimated glucose disposal rate (eGDR) and estimated insulin sensitivity (eIS) equations previously validated in adult T1D patients by the Pittsburgh Epidemiology of Diabetes Complications (EDC) (70) and Coronary Artery Calcification in Type 1 Diabetes (CACTI) studies (71), respectively. Other surrogate measures of insulin resistance included the previously validated visceral adiposity index (VAI) and the triglyceride (Tg)/HDL ratio calculated from the standard lipid profile by dividing Tg by HDL using values in units of mg/dL (72).

Inflammatory markers: Serum C-reactive protein (CRP) was measured by particle-enhanced immunonephelometry (BN ProSpec analyzer; Dade Behring, IL). Inflammatory cytokine (IFNγ, TNFα, IL6, IL1β) concentrations were measured in human plasma using the Meso Scientific Discovery Multiplex electrochemiluminescence assay (Maryland, USA) as per the protocol of the Proinflammatory Panel 1 (human) V-PLEX kit (Catalog No. K151A9H) and the plasma samples were diluted 2-fold.

CGM, Hypoglycemia and neuropathy assessments: Among existing continuous glucose monitor (CGM) users, a single consecutive 14-day block of CGM data was remotely obtained after a period of performing usual activities in a subset of the cognitive study participants (n=96). CGM indices of variability (CV), hyperglycemia (time-above-range, TAR>250 mg/dL) or hypoglycemia (time-below-range TBR < 70 mg/dL) were extracted. The COMPASS-31 questionnaire (73) assessed hypoglycemia severity and frequency and autonomic neuropathy, and the Clarke Hypoglycemia Awareness Survey (74) assessed hyoglycemia awareness. Peripheral neuropathy was adjudicated by the Michigan Screening Instrument (MNSI) survey score >2 (75, 76).

Advanced Glycation End-Products (AGEs): Carboxymethyl-lysine (CML), carboxyethyl-lysine (CEL), and methylglyoxal-hydroimidazolone-1 (MGH1) were measured using high-performance liquid chromatography mass spectrometry adapted from previously described methods (77).

Brain Imaging: Scanning was performed on a Siemens 3 Tesla Prism scanner at the Brigham and Women's Hospital imaging core as per the Alzheimer's Disease Neuroimaging Initiative 3 (ADNI) advanced protocol guidelines (Supplementary Table 9) (78). For patient comfort and flexibility to adjust for kyphosis that is more prevalent in older cohorts, the 32 channel GE head

coil was used. Structural volumetrics were acquired via the T1-weighted sequences and processed using Freesurfer image analysis suite (79). Regions of interest (ROIs) were derived by summing volumes of right and left hemispheres of various cortical and subcortical regions as described in Supplementary Table 10. Volumes of white matter hyperintensities (WMH) were extracted from the freesurfer output. Microbleeds and lacunar infarcts were manually counted in each individual brain scan by a board-certified neuroradiologist using the T2*GRE and 3D-FLAIR sequences. Arterial spin labeling (ASL) sequences assessed cerebral blood flow alterations.

Ocular assessments: These were performed at the Joslin Beetham Eye Institute, as previously described (13). Visual acuity was assessed using standardized Early Treatment Diabetic Retinopathy Study (ETDRS) chart (80). PDR was adjudicated at ETDRS score > 53 on 7-standard field fundus photos (81). Individual retinal layer thicknesses in the foveal 1x1mm area were measured by spectral-domain Optical Coherence Tomography (OCT)-based high resolution scans with automated layer segmentation software (SPECTRALIS v6.0; Heidelberg Engineering, Heidelberg, Germany). The following layers were evaluated: retinal nerve fiber (RNFL), ganglion cell (GCL), inner and outer plexiform (IPL and OPL), inner and outer nuclear (INL and ONL) and retinal pigment epithelium (RPE) (82).

Brain Gross and Histopathology: Over 400 Medalists have consented to donate organs post-mortem. Brains were procured from 26 Medalist donors by a trained retrieval team from the National Disease Research Interchange (NDRI, Philadelphia, PA). Fresh brains were examined for any grossly evident pathology (atrophy, focal and vascular lesions), then sagittally hemisected and formalin-fixed. A standard histopathological paraffin-embedded blocking procedure and hematoxylin/eosin staining was applied. Selected sections were immunostained

with antibodies directed toward beta-amyloid, tau and alpha-synuclein. Interpretation of vascular and neurodegenerative pathology followed standard guidelines (26, 27). Alzheimer's-related pathology was graded as per Braak staging (28). Under the supervision of our consultant neuropathologist, brain sectioning and histopathology was done at Brigham and Women's Hospital, Boston, MA.

For comparison of Medalists' brain weights with that of a normal aging population, summary level data were obtained from a previous study compiling brain weights from autopsy reports of 2,773 males and 1,963 females, who were all White subjects across the lifespan, from hospitals in D.C and MD (25). For our study comparison, mean (SD) brain weights of individuals aged 66+ were extracted for 546 males and 465 females (25).

Statistical analysis

All analyses were conducted in SAS v.9.4 (Cary, NC). Descriptive statistics reported as means (±SD) or frequencies (n, %) as appropriate. Differences between T1D Medalists and controls were examined via unpaired Student's t-tests for continuous variables, and Pearson's chi-square tests for independence applied to categorical variables. For non-normally distributed variables, data were log-transformed as appropriate or the Mann-Whitney U-test, a non-parametric alternative to the t-test, was used. Cross-sectional relationships of cognitive or imaging parameters with clinical characteristics were assessed using generalized linear regression models. Significant variables ($p<0.05$) from the bivariate analyses were selected as potential confounders in multivariable linear regression models testing relationships between cognitive and brain imaging parameters in T1D Medalists. Generalized linear regression models adjusting for intracranial volume (ICV) were applied to examine differences in brain imaging parameters between Medalists and controls. The equivalent years of age for volume differences between

Medalists and controls were obtained from linear regression models by calculating the ratio of the beta estimate for caseness to that for age when both variables and ICV were included as independent variables and MRI volumes were the dependent variables.

For illustration purposes, we used standardized estimates (where the estimates represent changes in the dependent variable per one standard deviation change in the independent variable) for the relationship between various clinical characters and cognitive functions or brain volumes. Then we used these estimates and respective p-values to plot heat maps where color and intensity represent the strength and direction (positive, zero or no, and negative) of association.

To evaluate the relationships between thickness of retinal nerve layers (derived by OCT) and cognitive or brain imaging parameters, we used generalized estimating equations with an unstructured correlation matrix accounting for within-subject correlations as data from both eyes of each individual were included in the model.

To assess the mediating effects of brain volume on the relationship between visual acuity or ONL thickness and psychomotor function, a mediation analysis was performed. The observed beta estimate (βobs) was derived from the linear regression model testing the effects of visual acuity on psychomotor function. The linear regression effect estimate (β1) of visual acuity (or ONL) on total brain volume (adjusted by ICV) was multiplied by the estimate (β2) derived from the linear regression between total brain volume and psychomotor function (with ICV and visual acuity as covariates), resulting in the expected beta (βexp). The expected β was divided by the observed (βexp / βobs) to derive the % mediation.

For the longitudinal analysis, paired t-tests were used to examine differences between cognitive function at first visit compared to follow-up visit. Change in cognitive function was derived by

subtracting the follow-up visit scores from the first visit scores for each domain, and linear regression models were applied to test the relationships between visual acuity from the first visit and change in cognitive function.

Study approval

The study followed written informed consent procedures, was conducted in accordance with the guidelines provided by the Declaration of Helsinki, and was overseen by the Joslin Committee on Human Studies institutional review board.

Data Availability

All datasets underlying the main and supplemental tables and figures have been made available in the uploaded document, "Shah_JCIinsight_Datasets.xlsx".

AUTHOR CONTRIBUTIONS

H.S.S. designed and conducted the study, acquired and analyzed data, and wrote the manuscript. M.D., A.H., S.J., R.R, A.H., T.B., L.N., A.A., Y.R., L.P.A. and M.B.F. analyzed data and reviewed the manuscript. M.G.Y, J.G., N.Z., E.V., I.W., K.P., W.F., T.C., J.S., acquired data and reviewed the manuscript. G.L.K. designed the study, acquired data, and wrote the manuscript.

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REFERENCES

1. CDC. National Diabetes Statistics Report, 2020. Centers for Disease Control and Prevention, U.S. Dept. of Human Health and Human Service, Atlanta, GA.
2. Biessels GJ, Staekenborg S, Brunner E, Brayne C, and Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol.* 2006;5(1):64-74.
3. Gudala K, Bansal D, Schifano F, and Bhansali A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. *J Diabetes Investig.* 2013;4(6):640-50.
4. American Diabetes A. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care.* 2013;36(4):1033-46.
5. Munshi MN. Cognitive Dysfunction in Older Adults With Diabetes: What a Clinician Needs to Know. *Diabetes Care.* 2017;40(4):461-7.
6. Kuo CL, Lu CL, Chang YH, and Li CY. Population-Based Cohort Study on Dementia Risk in Patients with Type 1 Diabetes Mellitus. *Neuroepidemiology.* 2018;50(1-2):57-62.
7. Brands AM, Biessels GJ, de Haan EH, Kappelle LJ, and Kessels RP. The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diabetes Care.* 2005;28(3):726-35.
8. Krolewski AS, Warram JH, and Freire MB. Epidemiology of late diabetic complications. A basis for the development and evaluation of preventive programs. *Endocrinology and metabolism clinics of North America.* 1996;25(2):217-42.
9. Lacy ME, Gilsanz P, Karter AJ, Quesenberry CP, Pletcher MJ, and Whitmer RA. Long-term Glycemic Control and Dementia Risk in Type 1 Diabetes. *Diabetes Care.* 2018;41(11):2339-45.
10. Lacy ME, Gilsanz P, Eng C, Beeri MS, Karter AJ, and Whitmer RA. Severe Hypoglycemia and Cognitive Function in Older Adults With Type 1 Diabetes: The Study of Longevity in Diabetes (SOLID). *Diabetes Care.* 2020;43(3):541-8.
11. Moheet A, Mangia S, and Seaquist ER. Impact of diabetes on cognitive function and brain structure. *Ann N Y Acad Sci.* 2015;1353:60-71.
12. Biessels GJ, and Reijmer YD. Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI? *Diabetes.* 2014;63(7):2244-52.
13. Fickweiler W, Wolfson EA, Paniagua SM, Yu MG, Adam A, Bahnam V, et al. Association of Cognitive Function and Retinal Neural and Vascular Structure in Type 1 Diabetes. *J Clin Endocrinol Metab.* 2021;106(4):1139-49.
14. Simo R, Stitt AW, and Gardner TW. Neurodegeneration in diabetic retinopathy: does it really matter? *Diabetologia.* 2018;61(9):1902-12.
15. Pedersen FN, Stokholm L, Lois N, Yang D, Cheung CY, Biessels GJ, et al. Structural and Metabolic Retinal Changes Associated With Mild Cognitive Impairment in Type 2 Diabetes. *Diabetes.* 2023;72(12):1853-63.
16. Little K, Llorian-Salvador M, Scullion S, Hernandez C, Simo-Servat O, Del Marco A, et al. Common pathways in dementia and diabetic retinopathy: understanding the mechanisms of diabetes-related cognitive decline. *Trends Endocrinol Metab.* 2022;33(1):50-71.
17. Vujosevic S, Aldington SJ, Silva P, Hernandez C, Scanlon P, Peto T, et al. Screening for diabetic retinopathy: new perspectives and challenges. *Lancet Diabetes Endocrinol.* 2020;8(4):337-47.
18. Gordin D, Shah H, Shinjo T, St-Louis R, Qi W, Park K, et al. Characterization of Glycolytic Enzymes and Pyruvate Kinase M2 in Type 1 and 2 Diabetic Nephropathy. *Diabetes Care.* 2019.
19. Keenan HA, Costacou T, Sun JK, Doria A, Cavellerano J, Coney J, et al. Clinical factors associated with resistance to microvascular complications in diabetic patients of extreme disease duration: the 50-year medalist study. *Diabetes Care.* 2007;30(8):1995-7.

20. Keenan HA, Sun JK, Levine J, Doria A, Aiello LP, Eisenbarth G, et al. Residual insulin production and pancreatic ss-cell turnover after 50 years of diabetes: Joslin Medalist Study. *Diabetes.* 2010;59(11):2846-53.
21. Qi W, Keenan HA, Li Q, Ishikado A, Kannt A, Sadowski T, et al. Pyruvate kinase M2 activation may protect against the progression of diabetic glomerular pathology and mitochondrial dysfunction. *Nat Med.* 2017;23(6):753-62.
22. Sun JK, Keenan HA, Cavallerano JD, Asztalos BF, Schaefer EJ, Sell DR, et al. Protection from retinopathy and other complications in patients with type 1 diabetes of extreme duration: the joslin 50-year medalist study. *Diabetes Care.* 2011;34(4):968-74.
23. Tinsley LJ, Kupelian V, D'Eon SA, Pober D, Sun JK, King GL, et al. Association of Glycemic Control With Reduced Risk for Large-Vessel Disease After More Than 50 Years of Type 1 Diabetes. *J Clin Endocrinol Metab.* 2017;102(10):3704-11.
24. Musen G, Tinsley LJ, Marcinkowski KA, Pober D, Sun JK, Khatri M, et al. Cognitive Function Deficits Associated With Long-Duration Type 1 Diabetes and Vascular Complications. *Diabetes Care.* 2018;41(8):1749-56.
25. Dekaban AS. Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. *Ann Neurol.* 1978;4(4):345-56.
26. Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement.* 2012;8(1):1-13.
27. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology.* 2005;65(12):1863-72.
28. Braak H, and Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol.* 1991;82(4):239-59.
29. Biessels GJ, and Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol.* 2018;14(10):591-604.
30. Pruzin JJ, Nelson PT, Abner EL, and Arvanitakis Z. Review: Relationship of type 2 diabetes to human brain pathology. *Neuropathol Appl Neurobiol.* 2018;44(4):347-62.
31. Jacobson AM, Braffett BH, Erus G, Ryan CM, Biessels GJ, Luchsinger JA, et al. Brain Structure Among Middle-aged and Older Adults With Long-standing Type 1 Diabetes in the DCCT/EDIC Study. *Diabetes Care.* 2022;45(8):1779-87.
32. Ryan CM. Effects of Diabetes Mellitus on Neuropsychological Functioning: A Lifespan Perspective. *Semin Clin Neuropsychiatry.* 1997;2(1):4-14.
33. Diabetes C, Complications Trial/Epidemiology of Diabetes I, Complications Study Research G, Jacobson AM, Musen G, Ryan CM, et al. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med.* 2007;356(18):1842-52.
34. Reichard P, Pihl M, Rosenqvist U, and Sule J. Complications in IDDM are caused by elevated blood glucose level: the Stockholm Diabetes Intervention Study (SDIS) at 10-year follow up. *Diabetologia.* 1996;39(12):1483-8.
35. Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. *Ann Intern Med.* 1996;124(4):379-88.
36. Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, Murray AM, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol.* 2011;10(11):969-77.
37. Savelieff MG, Chen KS, Elzinga SE, and Feldman EL. Diabetes and dementia: Clinical perspective, innovation, knowledge gaps. *J Diabetes Complications.* 2022;36(11):108333.

38. Biessels GJ, and Reagan LP. Hippocampal insulin resistance and cognitive dysfunction. *Nat Rev Neurosci.* 2015;16(11):660-71.
39. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Nat Rev Neurol.* 2018;14(3):168-81.
40. Beckman JA, and Creager MA. Vascular Complications of Diabetes. *Circ Res.* 2016;118(11):1771-85.
41. Basta G, Schmidt AM, and De Caterina R. Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. *Cardiovasc Res.* 2004;63(4):582-92.
42. Habes M, Jacobson AM, Braffett BH, Rashid T, Ryan CM, Shou H, et al. Patterns of Regional Brain Atrophy and Brain Aging in Middle- and Older-Aged Adults With Type 1 Diabetes. *JAMA Netw Open.* 2023;6(6):e2316182.
43. McArdle JJ, Fisher GG, and Kadlec KM. Latent variable analyses of age trends of cognition in the Health and Retirement Study, 1992-2004. *Psychol Aging.* 2007;22(3):525-45.
44. Downer B, Fardo DW, and Schmitt FA. A Summary Score for the Framingham Heart Study Neuropsychological Battery. *J Aging Health.* 2015;27(7):1199-222.
45. Moran C, Gilsanz P, Beeri MS, Whitmer RA, and Lacy ME. Sex, diabetes status and cognition: findings from the study of longevity in diabetes. *BMJ Open Diabetes Res Care.* 2021;9(1).
46. Nebel RA, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, et al. Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimers Dement.* 2018;14(9):1171-83.
47. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2022;18(4):700-89.
48. Chatterjee S, Peters SA, Woodward M, Mejia Arango S, Batty GD, Beckett N, et al. Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia. *Diabetes Care.* 2016;39(2):300-7.
49. Krivanek TJ, Gale SA, McFeeley BM, Nicastri CM, and Daffner KR. Promoting Successful Cognitive Aging: A Ten-Year Update. *J Alzheimers Dis.* 2021;81(3):871-920.
50. Mirzaei N, Shi H, Oviatt M, Doustar J, Rentsendorj A, Fuchs DT, et al. Alzheimer's Retinopathy: Seeing Disease in the Eyes. *Front Neurosci.* 2020;14:921.
51. Kern TS, and Berkowitz BA. Photoreceptors in diabetic retinopathy. *J Diabetes Investig.* 2015;6(4):371-80.
52. Lindenberger U, and Baltes PB. Sensory functioning and intelligence in old age: a strong connection. *Psychol Aging.* 1994;9(3):339-55.
53. Gaire BP, Koronyo Y, Fuchs DT, Shi H, Rentsendorj A, Danziger R, et al. Alzheimer's disease pathophysiology in the Retina. *Prog Retin Eye Res.* 2024;101:101273.
54. Zheng DD, Swenor BK, Christ SL, West SK, Lam BL, and Lee DJ. Longitudinal Associations Between Visual Impairment and Cognitive Functioning: The Salisbury Eye Evaluation Study. *JAMA Ophthalmol.* 2018;136(9):989-95.
55. Clemons TE, Rankin MW, McBee WL, and Age-Related Eye Disease Study Research G. Cognitive impairment in the Age-Related Eye Disease Study: AREDS report no. 16. *Arch Ophthalmol.* 2006;124(4):537-43.
56. Anstey KJ, Luszcz MA, and Sanchez L. Two-year decline in vision but not hearing is associated with memory decline in very old adults in a population-based sample. *Gerontology.* 2001;47(5):289-93.

57. Strauss E, Sherman EMS, and Spreen O. *A compendium of neuropsychological tests: Administration, norms, and commentary, 3rd ed.* New York, NY, US: Oxford University Press; 2006.
58. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005;53(4):695-9.
59. Damian AM, Jacobson SA, Hentz JG, Belden CM, Shill HA, Sabbagh MN, et al. The Montreal Cognitive Assessment and the mini-mental state examination as screening instruments for cognitive impairment: item analyses and threshold scores. *Dement Geriatr Cogn Disord.* 2011;31(2):126-31.
60. Paffenbarger RS, Jr., Wing AL, and Hyde RT. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol.* 1978;108(3):161-75.
61. Carlson MC, Parisi JM, Xia J, Xue QL, Rebok GW, Bandeen-Roche K, et al. Lifestyle activities and memory: variety may be the spice of life. The women's health and aging study II. *J Int Neuropsychol Soc.* 2012;18(2):286-94.
62. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol.* 1985;122(1):51-65.
63. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, and Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol.* 1992;135(10):1114-26; discussion 27-36.
64. Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, and Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation.* 2009;119(8):1093-100.
65. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, and Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. *Arch Intern Med.* 2008;168(7):713-20.
66. Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, Bennett DA, et al. MIND diet slows cognitive decline with aging. *Alzheimers Dement.* 2015;11(9):1015-22.
67. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, and Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimers Dement.* 2015;11(9):1007-14.
68. Lee DH, Li J, Li Y, Liu G, Wu K, Bhupathiraju S, et al. Dietary Inflammatory and Insulinemic Potential and Risk of Type 2 Diabetes: Results From Three Prospective U.S. Cohort Studies. *Diabetes Care.* 2020;43(11):2675-83.
69. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012;367(1):20-9.
70. Williams KV, Erbey JR, Becker D, Arslanian S, and Orchard TJ. Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes.* 2000;49(4):626-32.
71. Duca LM, Maahs DM, Schauer IE, Bergman BC, Nadeau KJ, Bjornstad P, et al. Development and Validation of a Method to Estimate Insulin Sensitivity in Patients With and Without Type 1 Diabetes. *J Clin Endocrinol Metab.* 2016;101(2):686-95.
72. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al. Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care.* 2010;33(4):920-2.
73. Sletten DM, Suarez GA, Low PA, Mandrekar J, and Singer W. COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. *Mayo Clin Proc.* 2012;87(12):1196-201.
74. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, and Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care.* 1995;18(4):517-22.

75. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, and Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes Care.* 1994;17(11):1281-9.
76. Herman WH, Pop-Busui R, Braffett BH, Martin CL, Cleary PA, Albers JW, et al. Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in Type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. *Diabet Med.* 2012;29(7):937-44.
77. Beisswenger PJ, Howell SK, Russell G, Miller ME, Rich SS, and Mauer M. Detection of diabetic nephropathy from advanced glycation endproducts (AGEs) differs in plasma and urine, and is dependent on the method of preparation. *Amino Acids.* 2014;46(2):311-9.
78. Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Green RC, et al. The Alzheimer's Disease Neuroimaging Initiative 3: Continued innovation for clinical trial improvement. *Alzheimers Dement.* 2017;13(5):561-71.
79. Fischl B. FreeSurfer. *Neuroimage.* 2012;62(2):774-81.
80. Ferris FL, 3rd, and Bailey I. Standardizing the measurement of visual acuity for clinical research studies: Guidelines from the Eye Care Technology Forum. *Ophthalmology.* 1996;103(1):181-2.
81. Aiello LP, Odia I, Glassman AR, Melia M, Jampol LM, Bressler NM, et al. Comparison of Early Treatment Diabetic Retinopathy Study Standard 7-Field Imaging With Ultrawide-Field Imaging for Determining Severity of Diabetic Retinopathy. *JAMA Ophthalmol.* 2019;137(1):65-73.
82. Aumann S, Donner S, Fischer J, and Muller F. In: Bille JF ed. *High Resolution Imaging in Microscopy and Ophthalmology: New Frontiers in Biomedical Optics*. Cham (CH); 2019:59-85.

FIGURE LEGENDS

Figure 1. Associations of clinical characteristics with cognitive function in T1D [n=222]. Heatmaps showing bivariate standardized estimates of associations between clinical characters as independent variables and cognitive function domains as dependent variables in linear regression models. The estimates represent changes in cognitive function per one standard deviation change in the clinical predictor. Color and intensity represent the strength and direction (positive, zero or no, and negative) of association. Better cognitive function is represented by more blue estimates, and worse by red. MIS=Memory index score. Blank squares not significant. ***p<0.0001, **p<0.01, *p<0.05. **1A.** Markers of sociodemographics and lifestyle. **1B.** Glycemic markers. Life.Hypog=lifetime hypoglycemia severity; CV=co-efficient of variation of glucose on CGM; TAR>250=time above range of glucose > 250 mg/dL; TIR 70-180=time-in-range 70-180 mg/dL; TBR<70=time below range of glucose <70 mg/dL; CEL, CML and MGH1 are advanced glycation end-products. **1C.** Cardiometabolic markers. DBP, SBP are diastolic and systolic blood pressure; CRP=C-reactive protein; IL=Interleukin; IFNγ=Interferon-gamma; TNFα=Tumor necrosis factor-alpha. **1D.** Insulin resistance markers. BMI=body mass index; eGDR=estimated glucose disposal rate. eIS=estimated insulin sensitivity. VAI=visceral adiposity index; TG:HDL=triglyceride:HDL ratio; WHR=waist-hip ratio. **1E.** Complications. ACR=Urine albumin-creatinine ratio; eGFR=estimated glomerular filtration rate; DN=diabetic nephropathy; RHA=reduced hypoglycemia awareness; DPN=diabetic peripheral neuropathy; AN=autonomic neuropathy; CVD=cardiovascular disease; CAC=coronary artery calcification; VA=visual acuity; PDR=proliferative diabetic retinopathy.

Figure 2. Brain structure and cognitive function in Medalists (T1D, n=52) vs. non-diabetic controls (NDM, n=20). 2A-B. Differences in brain volumes between T1D and NDM. Forest

plots showing beta estimates and 95% confidence intervals from linear regression associations between regional **(2A)** and total **(2B)** brain volumes and case (T1D) versus control (NDM) status, adjusted by intracranial volumes. Eq.yrs of age=equivalent years of aging of T1D brain compared to NDM. Alz.Ds.Sig.=Alzheimer's disease signature region. **2C-D.** Associations between brain volumes and cognitive function. Heatmaps showing bivariate standardized estimates of associations between brain volumes and cognitive function in T1D (**2C)** and NDM controls from linear regression models (**2D)**. Better cognitive function is represented by more blue estimates, and worse cognitive function by red. MIS=Memory index score. Deep_GM=deep gray matter; Blank squares not significant. ***p<0.0001, **p<0.01, *p<0.05.

Figure 3. Associations of clinical characteristics with brain volumes in T1D [n=52]. Heatmaps showing bivariate standardized estimates of associations between clinical characters as independent variables and brain volumes as dependent variables from linear regression models. The estimates represent changes in brain volume per one standard deviation change in the clinical predictor. Color and intensity represent the strength and direction (positive, zero or no, and negative) of association. Higher brain volume is represented by more blue estimates, and lower by red. Blank squares not significant. ***p<0.0001, **p<0.01, *p<0.05. **3A.** Markers of sociodemographics and lifestyle. **3B.** Glycemic markers. Life.Hypog=lifetime hypoglycemia severity; CV=co-efficient of variation of glucose on CGM; TAR>250=time above range of glucose > 250 mg/dL; TIR 70-180=time-in-range 70-180 mg/dL; TBR<70=time below range of glucose <70 mg/dL; CEL, CML and MGH1 are advanced glycation end-products. **3C.** Cardiometabolic markers. DBP, SBP are diastolic and systolic blood pressure; CRP=C-reactive protein; IL=Interleukin; IFNγ=Interferon-gamma; TNFα=Tumor necrosis factor-alpha. **3D.** Insulin resistance markers. BMI=body mass index; eGDR=estimated glucose disposal rate.

eIS=estimated insulin sensitivity. VAI=visceral adiposity index; TG:HDL=triglyceride:HDL ratio; WHR=waist-hip ratio. **3E.** Complications. ACR=Urine albumin-creatinine ratio; eGFR=estimated glomerular filtration rate; DN=diabetic nephropathy; RHA=reduced hypoglycemia awareness; DPN=diabetic peripheral neuropathy; AN=autonomic neuropathy; CVD=cardiovascular disease; CAC=coronary artery calcification; VA=visual acuity; PDR=proliferative diabetic retinopathy.

Figure 4. Vascular imaging in Medalists (T1D, n=52) versus non-diabetic (NDM, n=20) controls. Differences between T1D and NDM for counts of microbleeds (**4A)** and lacunar infarcts (**4B)**, volume of white matter hyperintensities (WMH) (**4C)** and regional cerebral perfusion (**4D).** Dot-plots show mean ±SD error bars. Mann-Whitney U-tests were used to test for significant differences in microbleeds and lacunar infarcts. WMH volumes were log-normalized and then differences were examined by student's t-test. Linear regression models tested for relationship between cerebral perfusion and case-control status, beta estimates and 95% confidence intervals are shown in the forest plot.

Figure 5. Gross and histopathological exams of 26 brains from T1D Medalists. 5A. Causes of death among 26 brain donors. CVD=Cardiovascular disease. **5B.** Distribution of brain weights in Medalists. Error bars represent means±SD. **5C.** Comparison of mean (±SD) brain weights for T1D Medalists (N=19 males and 7 females) compared to summary data from normal referenced aging population (N=546 males and 465 females). ***$p<0.0001$, **$p<0.01$, *$p<0.05$ from standardized t-tests. **5D.** Arteriolosclerosis and Alzheimer's pathology. Hematoxylin and eosin (H&E) staining of normal vessel with thin wall (upper left, arrow), mild arteriolosclerosis with thickening of vessel wall and widened perivascular space (upper middle), and moderate-to-severe arteriolosclerosis with thickened vessel wall and surrounding parenchymal damage (upper

right). Scale bar is 50 microns. Immunohistochemistry (IHC) staining of amyloid plaque (lower left, arrow), neurofibrillary tangle (lower middle, arrow) and vessel involved by cerebral amyloid angiopathy (lower right, arrow). **5E.** Summary of brain gross and histopathological exams (n=26).

Figure 6. Relationships between Outer nuclear layer (ONL) thickness, visual acuity and brain volumes in T1D (n=52). 6A. ONL thickness and brain volumes in T1D**.** Linear regression beta estimates and 95% confidence intervals shown in forest plot. Alz.Ds.Sig.=Alzheimer's disease signature region. Deep_GM=deep gray matter. **6B-C.** Mediation analysis. Estimating how much of the association between visual acuity (**6B)** or ONL thickness (**6C)** and brain volume is mediated by psychomotor function. Each arrow represents a linear regression model with the dependent variable at the arrowhead and the independent variable at the arrow base. βobs=observed beta; βexp=expected beta; SE=standard error.

Table 1. Cross-sectional characteristics of study participants

Characteristic	Medalists with Cognitive data (N=222)	Medalists with brain MRI (N=52)	Non-diabetic Controls with brain MRI (N=20)	Longitudinal subset at first cognitive visit (N=48)	Brain donors at last clinical visit (N=26)
Females, N (%)	116 (52.3)	24 (46.2)	10 (50.0)	25 (52.1)	7 (26.9)
Current Age (years)	71.2 (7.1)	72.4 (6.2)	70.0 (7.6)	67.7 (6.9)	N/A
Duration of disease at visit or death (years)	60.9 (6.5)	62.5 [60-67.0]	N/A	54.9 (4.5)	68.3 (6.7)
Age at Diagnosis (years)	10.4 (5.9)	9.0 (4.81)	N/A	10.5 (5.5)	14.3 (6.5)
Age at death (years)	N/A	N/A	N/A	N/A	82.6 (7.0)
Time between last visit and death (years)	N/A	N/A	N/A	N/A	8.1 (4.3)
HbA1c (%) ***	6.8 (0.8)	6.6 (0.70)	5.4 (0.3)	6.9 (0.7)	7.3 (1.0)
Body mass index (kg/m^2)	26.2 (5.8)	26.2 (5.1)	26.4 (2.8)	25.6 (4.0)	25.1 (3.6)
Diastolic blood pressure (mmHg) *	66.1 (7.2)	66.5 (7.2)	70.7 (8.9)	64.6 (6.8)	65.2 (9.8)
Systolic blood pressure (mmHg) *	138.2 (17.8)	141.5 (15.2)	129.8 (11.9)	131.8 (13.8)	140.2 (18.4)
Hypertension, N (%)*	174 (81.3)	37 (72.6)	9 (47.4)	31 (64.6)	21 (80.8)
Total cholesterol (mg/dL)*	157.1 (34.8)	158.3 (37.3)	185.2 (44.1)	162.3 (32.1)	153.0 (34.6)
HDLc (mg/dL)	65.8 (18.1)	66.1 (17.0)	58.9 (15.6)	68.2 (19.5)	61.2 (18.8)
LDLc (mg/dL) **	76.6 (26.1)	78.2 (29.0)	108.4 (37.4)	79.8 (24.8)	74.4 (25.0)
Triglycerides (mg/dL)	63.0 [51.0-79.0]	61.0 [51.0-73.5]	70.5 [57.5-112.5]	61.0 [48.5-77.0]	59.5 [48.0-96.0]
eGFR (ml/min/1.73m^2), N (%)	70.3 (20.8)	73.0 (19.3)	75.9 (15.5)	75.7 (16.4)	62.3 (27.8)
ACR (ug/mg)	11.0 [6.0-33.0]	11.0 [7.0-79.0]	5.0 [3.0-14.0]	8.0 [5.0-23.0]	18 [10.0-54.9]
DN (eGFR <45 ml/min/1.73m^2), N (%)	24 (11.0)	4 (7.7)	N/A	3 (6.3)	7 (26.9)

CVD, N (%)	95 (43.2)	18 (34.6)	4 (22.2)	19 (39.6)	17 (65.4)
PDR (ETDRS>53), N (%)	75 (47.8)	18 (40.0)	N/A	18 (40.9)	9 (34.6)
Neuropathy (MNSI≥2), N (%)	98 (62.8)	30 (57.7)	N/A	15 (62.5)	12 (46.2)
Report ever smoking, N (%)	89 (41.6)	17 (33.3)	7 (36.8)	22 (45.8)	13 (52.0)
Report physical activity, N (%)	174 (80.9)	42 (80.8)	13 (76.4)	43 (89.6)	20 (76.9)
Education: college or higher, N (%)	174 (79.8)	45 (88.2)	17 (94.4)	33 (77.1)	21 (80.8)
Cognitive function[#]					
Working memory	10.7 (2.8)	11.2 (2.5)	11.4 (2.0)	10.4 (2.9)	10.8 (2.2)
Executive function	9.9 (3.0)	10.1 (3.4)	11.6 (2.7)	10.6 (3.1)	7.5 (5.9)
Immediate recall	52.2 (14.7)	51.2 (17.3)	56.4 (12.0)	53.2 (15.1)	52.8 (13.0)
Delayed recall*	48.8 (15.8)	47.8 (16.4)	60.2 (12.3)	48.0 (22.2)	49.17 (11.6)
Psychomotor skills (D)***	135.4 (90.1)	135.7 (62.5)	87.9 (12.7)	136.75 (124.4)	140 (43.5)
Psychomotor skills (ND)**	161.0 (120.6)	168.3 (140.4)	95.4 (20.0)	145.75 (89.1)	169 (85.7)
Global cognition (mis)*	11.4 (3.3)	11.6 (2.9)	13.3 (1.6)	N/A	N/A
Global cognition (total)**	26.0 (2.4)	26.1 (2.0)	28.1 (2.3)	N/A	N/A
Below Norm					
Immediate recall (<35), N (%)	16 (7.6)	6 (11.5)	1 (5.0)	5 (10.4)	0 (0)
Delayed recall (<35), N (%)*	41 (18.5)	13 (25.0)	0 (0)	14 (29.2)	0 (0)
Global Cognition (total) (<26), N (%)*	31 (34.8)	17 (33.3)	2 (10.5)	N/A	N/A

D, ND: Dominant and non-dominant hands; mis: Memory index score; eGFR: estimated glomerular filtration rate; ACR: Urine albumin creatinine ratio; PDR: proliferative diabetic retinopathy; CVD: cardiovascular disease; DN: diabetic nephropathy;

For continuous variables, means (SD) presented for normally distributed variables, and median (IQR) for non-normally distributed variables; Frequency, N (%) for categorical variables. N/A – data not available. For psychomotor skills, scores represent time to complete the groove pegboard test, higher scores mean worse motor function. For all other cognitive domains, higher scores represent better cognitive function. [#]Cognitive function for brain donor group, N=4.

***p<0.0001 **p<0.001 *p<0.05 for differences between Medalists and controls that underwent brain MRI.

Table 2. Characteristics of selected brain donors

Characteristic	Donor No.							
	8	**12**	**13**	**14**	**15**	**19**	**22**	**26**
Sex	M	M	M	M	M	M	F	M
Age at death	83	89	81	92	86	84	85	81
APOE	e4e4	e3e4	e2e3	e2e3	e3e3	e3e3	e3e3	e3e4
Cause of death	Respiratory Failure	Alzheimer's disease	CVD	CVD	Renal Failure	Accident	Alzheimer's disease	CVD
Clinical history at last visit								
HbA1c, %	7.5	7.5	5.1	6.2	7.0	6.7	8.5	6.5
CVD	yes	no	yes	yes	no	no	yes	yes
DN	no	yes	yes	no	yes	no	no	no
PDR	yes	no	.	yes	.	yes	.	no
Cognitive function at last visit								
Working memory			12.0	9.0	14.0	10.0		9.0
Executive function			4.0*	.	1.0*	12.0		13.0
Immediate recall			44.5	68.5	59.2	35.2*		56.5
Delayed recall			37.5*	50.0	58.3	37.5*		62.5
Psychomotor (D)			154.0*	.	121.0*	193.0*		92.0
Psychomotor (ND)			158.0*	.	134.0*	291.0*		93.0
Global cognition (total)			27	.	25*	.		.

Brain histopathology								
Brain weight (g)	1140	1100	1180	1080	1330	1150	1010	1390
Atrophy	mild	mild	mild	mild	no	mild	mild	mild
Vascular pathology								
Infarct	no	yes	yes	no	no	no	no	no
Hemorrhage	no	no	mvl	no	no	no	no	no
Arteriosclerosis	moderate	moderate	moderate-severe	moderate	moderate	mild-moderate	mild-moderate	mild-moderate
Atherosclerosis	mild	mild	mild	moderate	mild	mild	mild	moderate
Cerebral amyloid angiopathy	mild-moderate	moderate	no	mild	no	no	mild-moderate	mild-moderate
Alzheimer's related pathology								
Amyloid plaques	+++	++	NA	+	negative	++	+++	+
Braak Stage	IV	I-II	I	III	I	III-IV	V	I
Non-Alzheimer's pathology	negative	negative	negative	negative	negative	Neocortical Lewy body disease	negative	negative

* Cognitive scores deviate by 1.5 S.D of the control population means; CVD: cardiovascular disease; DN: diabetic nephropathy; PDR: proliferative diabetic retinopathy; mvl: micro-vascular lesions.

Amyloid plaques: +++ frequent; ++ moderate; + infrequent; NA- not assessed.

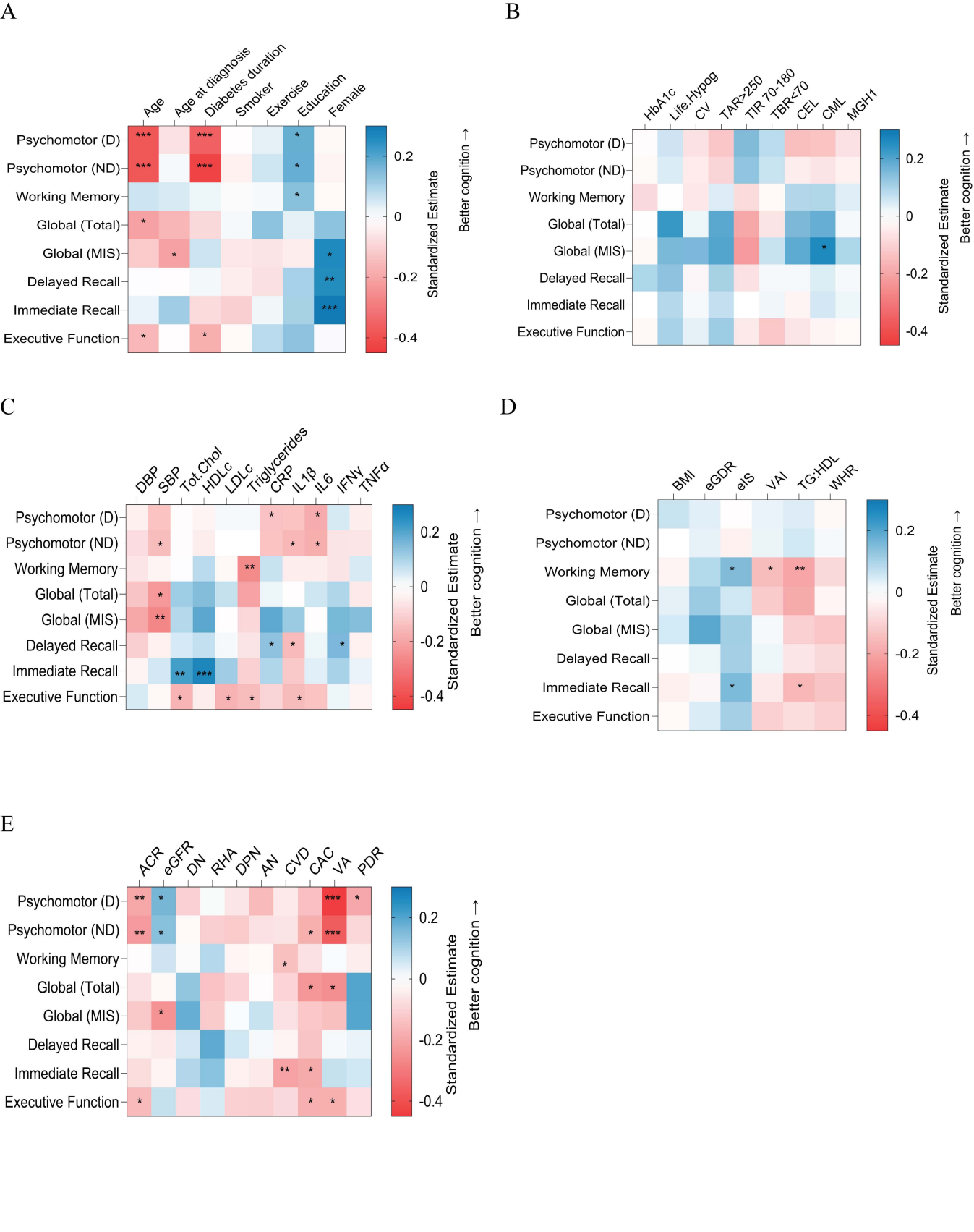

A
Age
Age at diagnosis
Diabetes duration
Smoker
Exercise
Education
Female
Psychomotor (D)
Psychomotor (ND)
Working Memory
Global (Total)
Global (MIS)
Delayed Recall
Immediate Recall
Executive Function
Standardized Estimate
Better cognition →
B
HbA1c
Life.Hypog
CV
TAR>250
TIR 70-180
TBR<70
CEL
CML
MGH1
C
DBP
SBP
Tot.Chol
HDLc
LDLc
Triglycerides
CRP
IL1β
IL6
IFNγ
TNFα
D
BMI
eGDR
eIS
VAI
TG:HDL
WHR
E
ACR
eGFR
DN
RHA
DPN
AN
CVD
CAC
VA
PDR

Figure 1

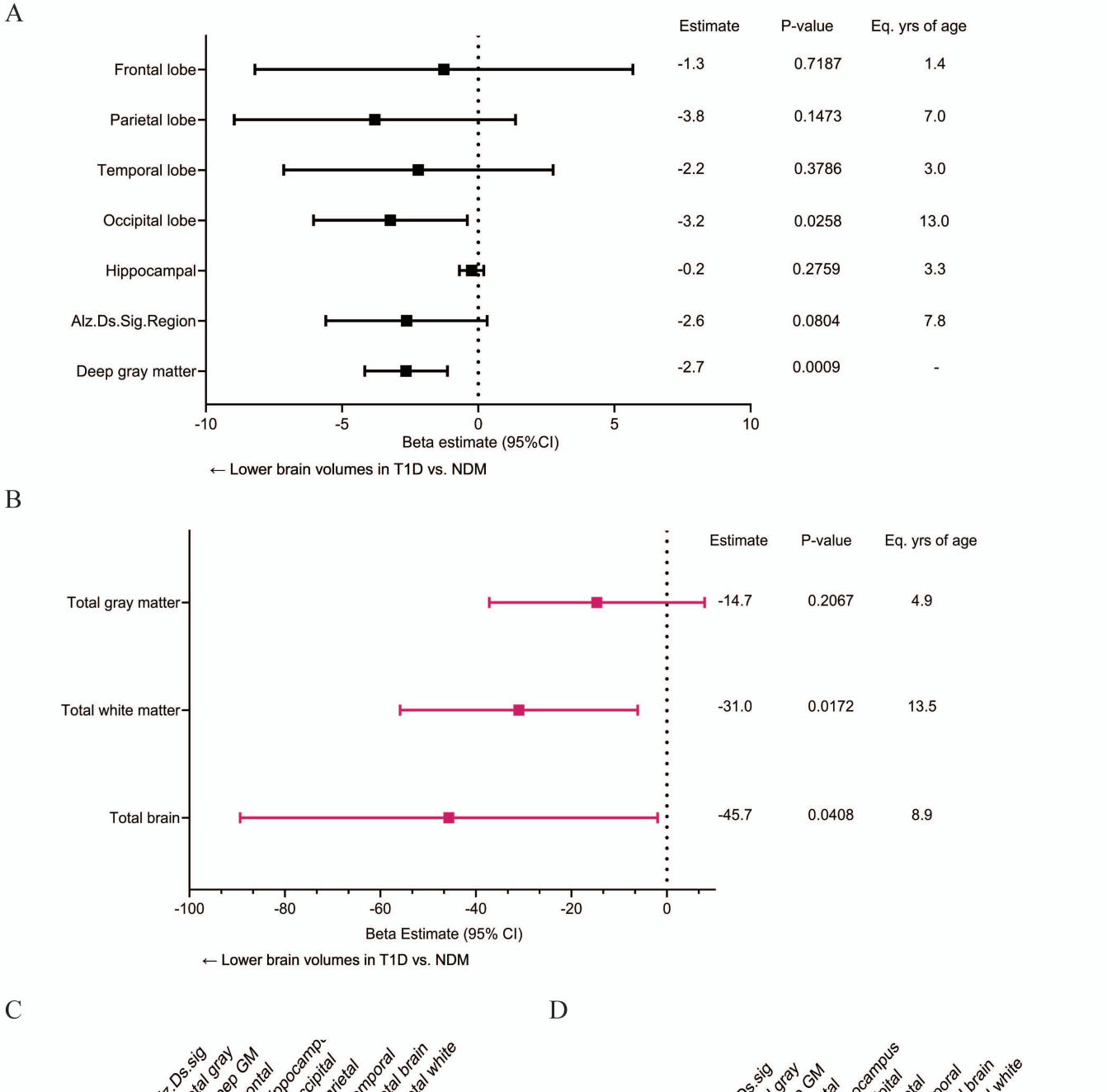

A
Estimate
P-value
Eq. yrs of age
Frontal lobe
-1.3
0.7187
1.4
Parietal lobe
-3.8
0.1473
7.0
Temporal lobe
-2.2
0.3786
3.0
Occipital lobe
-3.2
0.0258
13.0
Hippocampal
-0.2
0.2759
3.3
Alz.Ds.Sig.Region
-2.6
0.0804
7.8
Deep gray matter
-2.7
0.0009
-
-10
-5
0
5
10
Beta estimate (95%CI)
← Lower brain volumes in T1D vs. NDM
B
Estimate
P-value
Eq. yrs of age
Total gray matter
-14.7
0.2067
4.9
Total white matter
-31.0
0.0172
13.5
Total brain
-45.7
0.0408
8.9
-100
-80
-60
-40
-20
0
Beta Estimate (95% CI)
← Lower brain volumes in T1D vs. NDM
C
Alz.Ds.sig
Total gray
Deep GM
Frontal
Hippocamp-
Occipital
Parietal
Temporal
Total brain
Total white
Psychomotor (D)
Psychomotor (ND)
Working Memory
Global (Total)
Global (MIS)
Delayed Recall
Immediate Recall
Executive Function
0.5
0
Standardized Estimate
←Lower vol.
Higher vol. →
D
Alz.Ds.sig
Total gray
Deep GM
Frontal
Hippocampus
Occipital
Parietal
Temporal
Total brain
Total white
Psychomotor (D)
Psychomotor (ND)
Working Memory
Global (Total)
Global (MIS)
Delayed Recall
Immediate Recall
Executive Function
0.5
0
Standardized Estimate
←Lower vol.
Higher vol. →

Figure 2

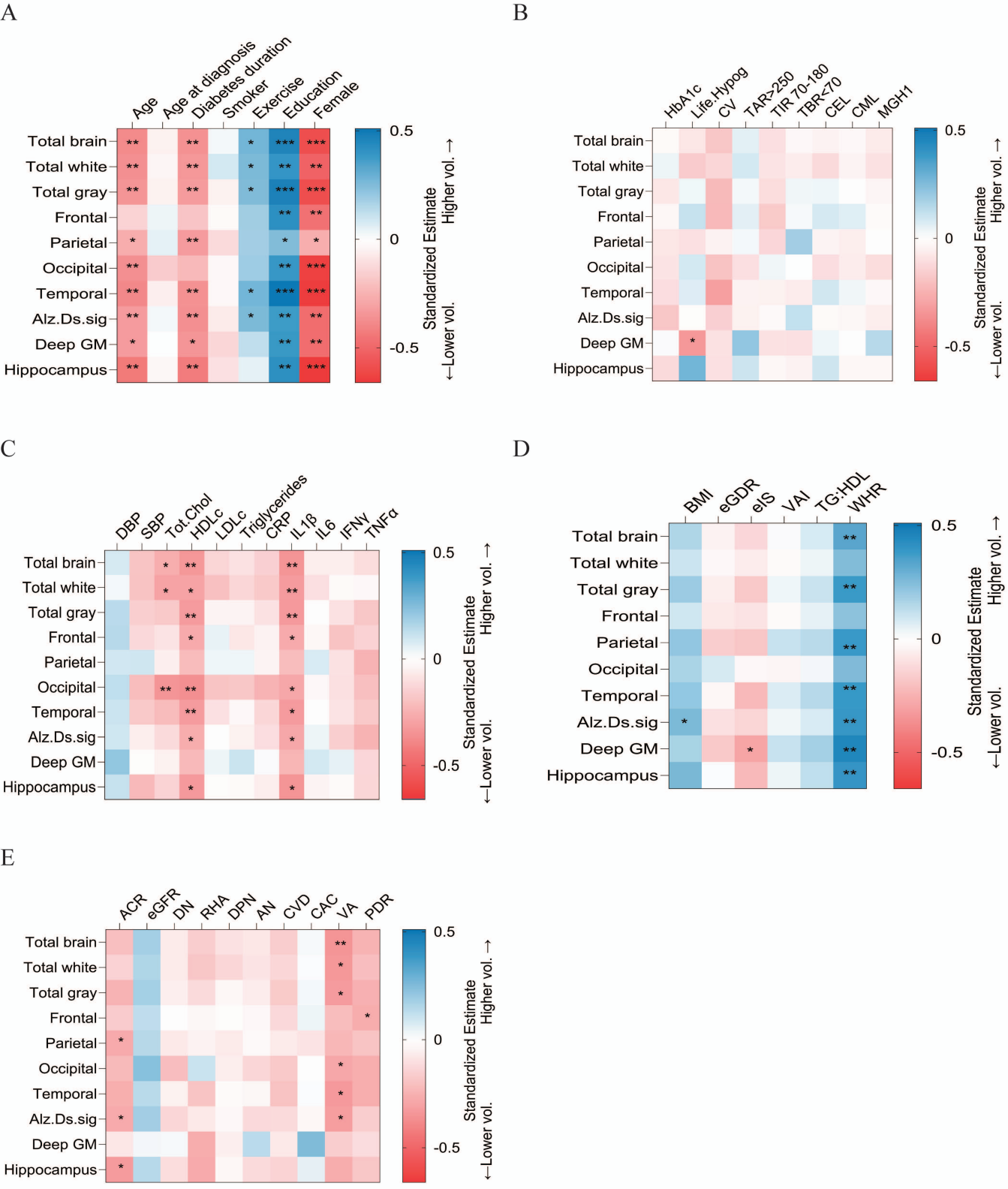
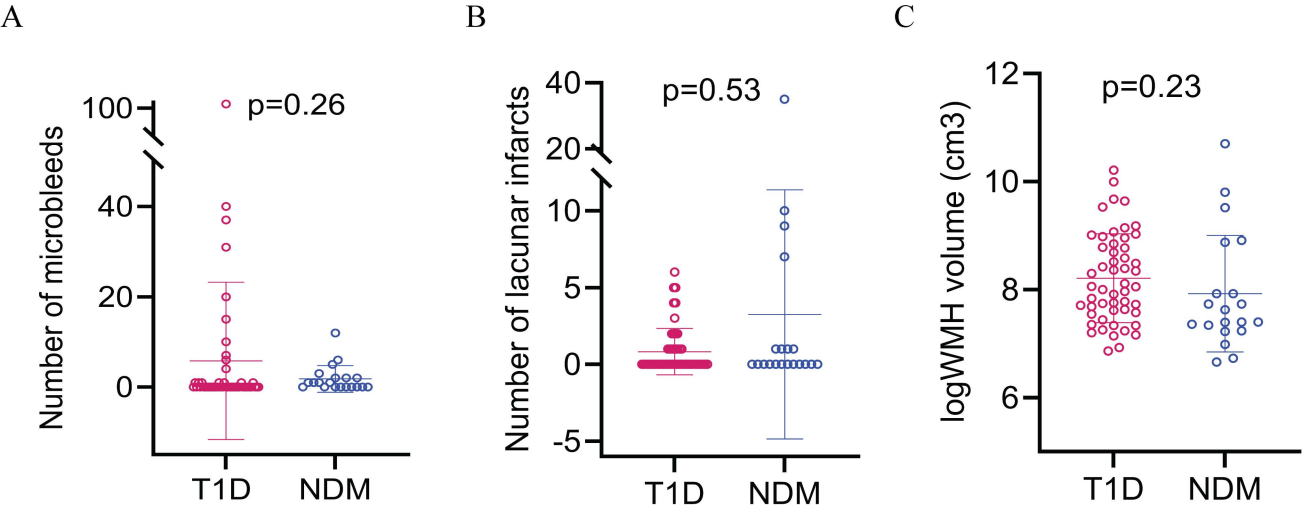

A
Age
Age at diagnosis
Diabetes duration
Smoker
Exercise
Education
Female
Total brain
Total white
Total gray
Frontal
Parietal
Occipital
Temporal
Alz.Ds.sig
Deep GM
Hippocampus
0.5
0
-0.5
Standardized Estimate
Higher vol. →
←Lower vol.
B
HbA1c
Life.Hypog
CV
TAR>250
TIR 70-180
TBR<70
CEL
CML
MGH1
C
DBP
SBP
Tot.Chol
HDLc
LDLc
Triglycerides
CRP
IL1β
IL6
IFNγ
TNFα
D
BMI
eGDR
eIS
VAI
TG:HDL
WHR
E
ACR
eGFR
DN
RHA
DPN
AN
CVD
CAC
VA
PDR

Figure 3


A
Number of microbleeds
100
40
20
0
p=0.26
T1D
NDM
B
Number of lacunar infarcts
40
20
10
5
0
-5
p=0.53
T1D
NDM
C
logWMH volume (cm3)
12
10
8
6
p=0.23
T1D
NDM

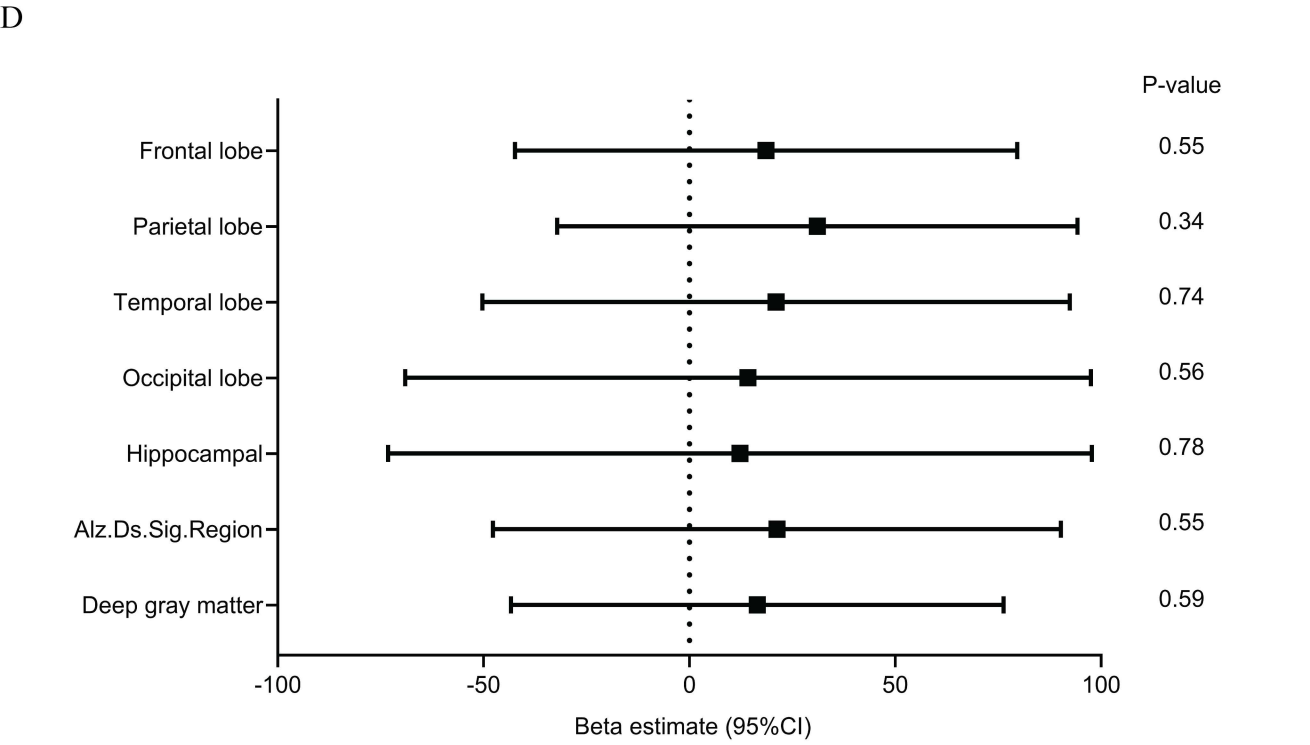

D
P-value
Frontal lobe
0.55
Parietal lobe
0.34
Temporal lobe
0.74
Occipital lobe
0.56
Hippocampal
0.78
Alz.Ds.Sig.Region
0.55
Deep gray matter
0.59
-100
-50
0
50
100
Beta estimate (95%CI)

Figure 4

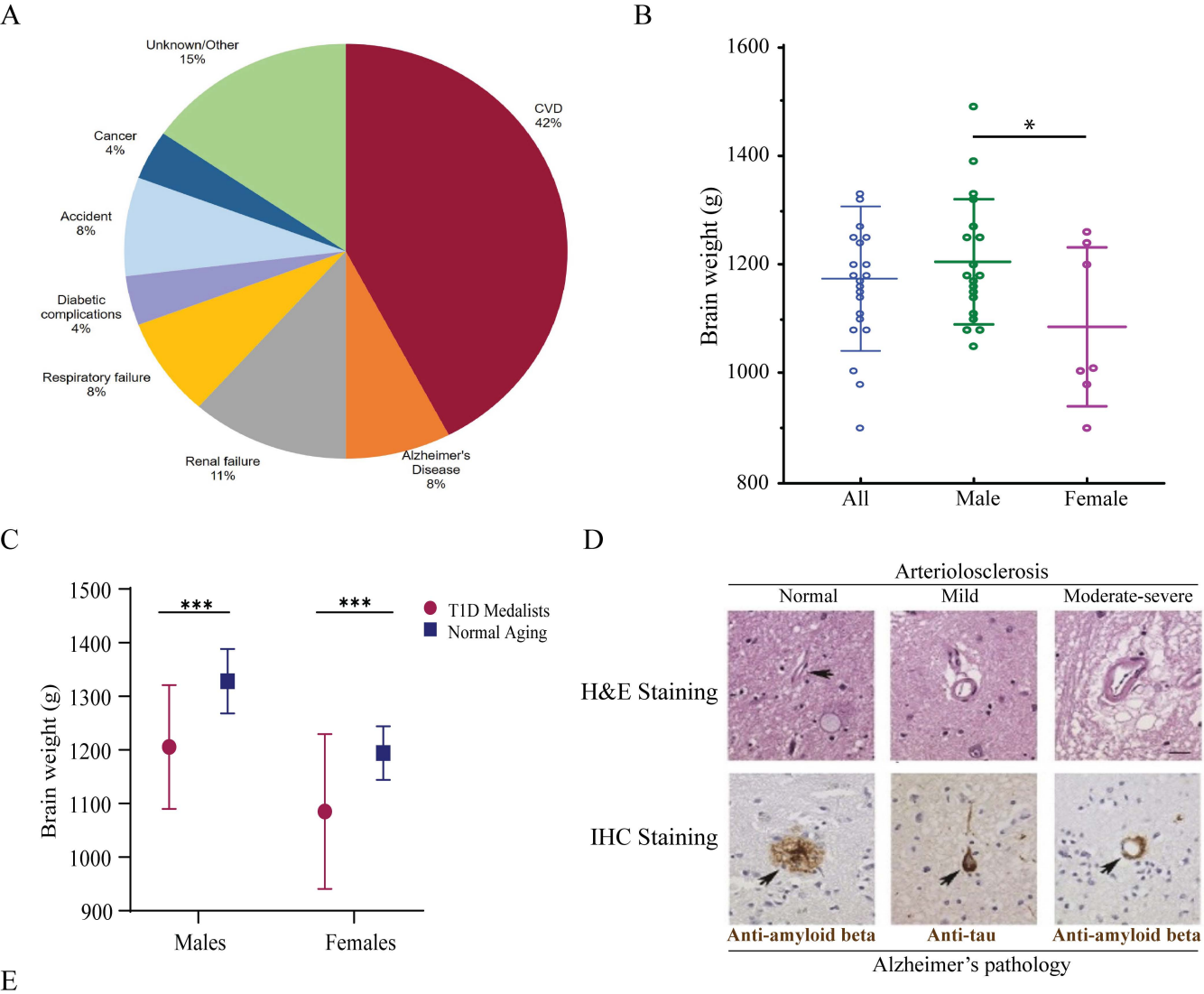
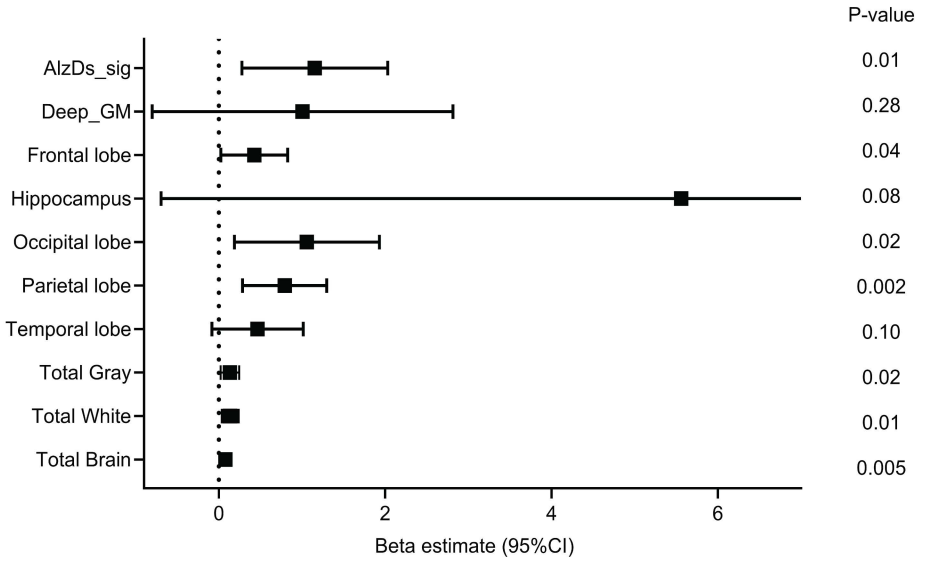
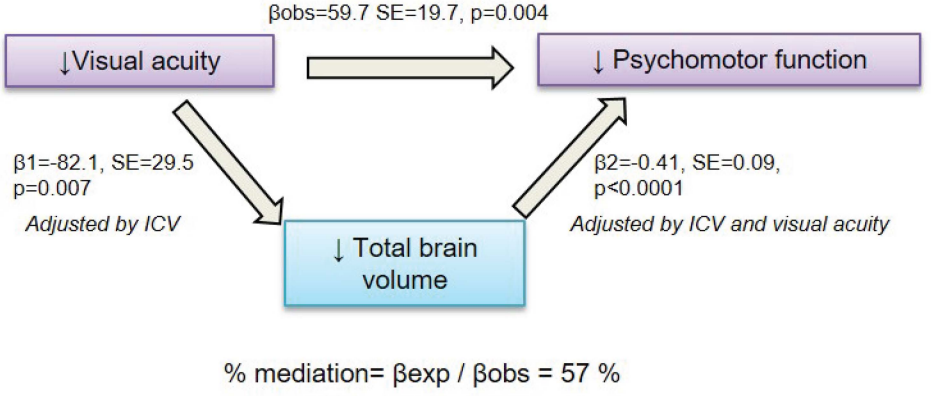

A
Unknown/Other
15%
CVD
42%
Cancer
4%
Accident
8%
Diabetic
complications
4%
Respiratory failure
8%
Renal failure
11%
Alzheimer's
Disease
8%
B
Brain weight (g)
1600
1400
1200
1000
800
*
All
Male
Female
C
Brain weight (g)
1500
1400
1300
1200
1100
1000
900
***
***
T1D Medalists
Normal Aging
Males
Females
D
Arteriolosclerosis
Normal
Mild
Moderate-severe
H&E Staining
IHC Staining
Anti-amyloid beta
Anti-tau
Anti-amyloid beta
Alzheimer's pathology
E
Atrophy
None
Mild
Mild-Moderate
Vascular
Infarcts
Hemorrhage
Arteriolosclerosis
None
Mild-Moderate
Moderate
Moderate-severe
Arterosclerosis
None
Mild
Moderate
Cerebral amyloid angiopathy
None
Mild-Moderate
Moderate
Alzheimer's related BRAAK staging
0
I-II
III-IV
IV-V
0%
10%
20%
30%
40%
50%
60%
70%

Figure 5

A

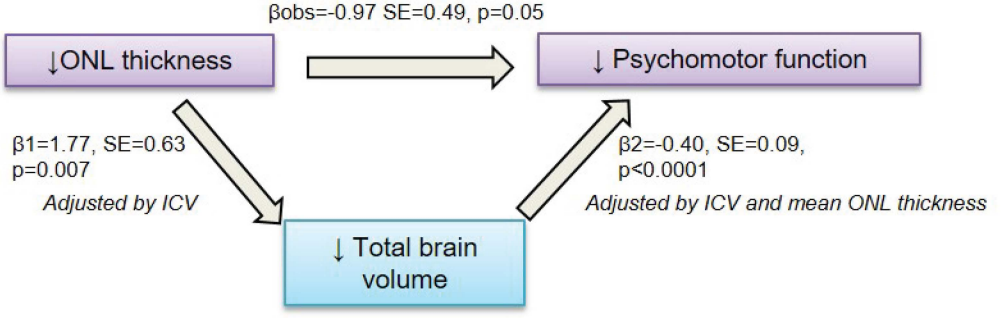


B



% mediation= βexp / βobs = 57 %

C



% mediation= βexp / βobs = 73 %

Figure 6