Title

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Locus of control and cognition in older adults with type I diabetes: evidence for sex differences from the Study of Longevity in Diabetes (SOLID)

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Abstract

Objective: Life expectancy for individuals with type 1 diabetes mellitus (T1DM) has increased recently; however, it is unknown how diabetes care attitudes affect late-life brain health.

Research design and methods: The Study of Longevity in Diabetes (SOLID) consists of 734 older adults with T1DM, reporting diabetes locus of control (dLOC), age of diabetes diagnosis and other demographics, history of hypoglycemic episodes, and depressive symptoms. Global and domain-specific (language, executive function, episodic memory, simple attention) cognitive functioning was assessed at in-person interviews. Cross-sectional associations between dLOC and cognition were estimated using covariate-adjusted linear regression models in pooled and sex-stratified models.

Results: In pooled analyses, a one-point increase in dLOC (more internal) was positively associated with global cognition (β=0.05, 95% CI: 0.02, 0.07), language (β=0.04, 95% CI: 0.01, 0.07), and executive function (β=0.04, 95% CI: 0.01, 0.07), but not episodic memory or simple attention. However, in sex-stratified analyses, this effect was seen only in males and not females.

Conclusions: In elderly individuals with T1DM, we found associations between dLOC and cognition overall and in men but not women. Underlying sex differences should be considered in future research or interventions on psychosocial characteristics for cognition.

Keywords

type 1 diabetes; locus of control; cognition; cognitive function; sex differences

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Introduction

As increases in life expectancy of the general population have been accompanied by concerns about the increasing burden of cognitive decline, recent large increases in life expectancy of older adults with type 1 diabetes mellitus[1,2] have highlighted a need for greater understanding of cognitive decline in this population as well.[3–6] Individuals with type 1 diabetes mellitus are at increased risk of cognitive deficits, for which the epidemiology differs from individuals without diabetes, though much of the research has focused on young or middle-aged adults.[7–9]

Health locus of control is a construct measuring beliefs in how one's health is influenced by oneself versus outside influences[10] with the latter representing attribution to outcomes of events to external forces beyond personal control. Health locus of control has previously been shown to be associated with cognition in otherwise healthy populations, with an inverse relationship between cognitive function and more external locus of control found in a sample of community dwelling older men in the US[11] and findings that changing from external to internal locus of control in midlife for women was more beneficial for cognition than remaining external or changing to become external.[12] Locus of control has also been found to be associated with amygdala functional connectivity in a small sample of cognitively healthy controls, suggesting a possible role of locus of control in cognitive aging.[13] However, little is known about how disease-specific locus of control in populations with conditions requiring high levels of care and attention, such as diabetes, may affect cognition.

Sex differences have also been observed for both locus of control and cognition. Women are more likely to have more external locus of control measures in general locus of control compared to men,[14] while studies of health locus of control have found that higher internal locus of control is significantly different between males and females in hemodialysis control measures with beneficial effects observed for women but not men.[15] Studies have also suggested that women are more likely to be diagnosed with dementia than men, although age and underlying pathology may affect the magnitude of these risks.[16,17]

To further disentangle the potential relationship between locus of control and cognition, we investigate the relationships between sex, diabetes-specific locus of control, and cognition in a cohort of older adults with type 1 diabetes, a condition requiring high levels of daily monitoring which individuals are likely to have lived with for decades prior to study enrollment. We do so by, first, characterizing the relationship between diabetes-specific locus of control (dLOC) and cognitive performance across multiple domains in older adults with type I diabetes. We, then, estimate sex-specific associations to assess for effect modification by sex on the relationship between diabetes-specific locus of control and cognitive functioning.

Methods

Study Participants

The Study of Longevity in Diabetes (SOLID) is a prospective cohort of individuals over the age of 60 with type 1 diabetes, with type 2 diabetes, or non-diabetic controls, designed with

the goal of understanding cognitive aging in individuals with diabetes. The analysis for this paper focused on only baseline measures of participants with type 1 diabetes mellitus. Potential participants were identified in electronic medical records using International Classification of Diseases (ICD)-9 and ICD-10 codes for T1D (250.x1, 250.x3, or E10.x) and T2D (250.x0, 250.x2, E11.x). Individuals with type 1 diabetes mellitus were classified if 75% or more diabetes-related codes were for type 1 diabetes mellitus and the member was prescribed insulin. Of the 2,113 KPNC members identified as eligible participants with type 1 diabetes mellitus, a total of 805 individuals with type 1 diabetes mellitus were enrolled and completed baseline surveys after exclusion at their home or a KPNC facility. For our analytic sample, we further excluded 28 participants with missing or refused responses to any of the locus of control components and an additional 43 with missing covariate information for an analytic sample size of 734 individuals with type 1 diabetes mellitus. All enrolled participants provided informed consent and this study was approved by the KPNC Internal Review Board.

Diabetes Locus of Control

dLOC was self-reported by participants through the mailed questionnaire using previously developed measures.[18] Participants ranked their level of agreement (strongly disagree, disagree, neutral, agree, strongly agree) on each of six statements depicting internal or external locus of control. Internal locus of control was measured using the following statements: “Taking care of my diabetes is a high priority for me right now”, “What I do has a big effect on my health”, and “I can avoid complications of diabetes”. External locus of control was measured using the following statements: “I have many more important things in my life than diabetes to take care of now”, “Good blood sugar control is a matter of luck”, and “My blood sugars will be what they will be”. Externally driven measures were reverse coded so that lower scores represented a belief in more external influence of diabetes management and higher scores represented more internal control of diabetes. Responses were summed and re-centered to a possible range of −12 to 12, with negative scale values representing a more external dLOC, positive values representing a more internal dLOC, and a value of zero representing a neutral dLOC (equivalent to answers of “neutral” on all 6 statements).

Cognition

Cognition was assessed through a comprehensive battery administered during in-person baseline interviews. A factor analysis revealed the following four cognitive domains: language, executive function, episodic memory, and simple attention. Language was measured using tests of phonemic fluency (F and L), category fluency (animals, vegetables), list sorting of two alternative lists, and Multilingual Naming Test (MINT). Executive function was measured using the Trail Making Test (A and B), Digit Symbol Substitution, and the Stroop Color and Word Test. Episodic memory was measured using the Word List Learning Test (immediate and delayed) and the Benson Complex Figure Copy (immediate and delayed). Attention was measured by the Diamond and TMX cancellation tests.

Domain-specific and global cognitive scores were estimated for individuals who completed at least 50% of the domain-specific tests or for global cognition, 50% of all tests combined.

Each cognitive domain and global cognition score was z-standardized to their respective sample mean and standard deviation, with a one-unit change representing one standard deviation.

Covariates

Sex was obtained from KPNC records and was identified *a priori* as a possible effect modifier of the relationship between dLOC and cognition. Models were adjusted for self-reported race (white versus non-white) and age in years at the time of the baseline interview. Age at diagnosis of type 1 diabetes mellitus was categorized as diagnosis <10 years of age (reference), 10 to 19 years, 20 to 39 years, and 40 years or older. Education was self-reported as highest level of degree attainment. History of hypoglycemic episodes was obtained by asking participants the number of times they had experienced a severe low blood sugar reaction such as passing out or needing help to treat reaction in their lifetime. This was dichotomized into a binary variable of any versus no episodes, as a measure of lifetime severe low blood sugar reaction preceding the measurement of locus of control and potential confounder of the relationship between locus of control and cognition. Participants also self-reported lifetime history of depressive symptoms (yes/no), in response to the following question: “In your lifetime, have you ever had 2 weeks or longer when nearly every day you felt sad, blue, depressed, or when you lost all interest in most things like work, hobbies, and other things you usually enjoyed?”.

Statistical Analysis

Distributions of all variables were examined overall as well as separately for males and females. The relationships between dLOC and cognition were estimated using separate multivariable linear regression models for each cognitive outcome (global cognition, language, episodic memory, executive functioning, and attention). Models sequentially controlled for (1) sex, race, and age at interview (model 1), (2) model 1 plus education, age at diabetes diagnosis, history of hypoglycemic episodes, and history of depressive symptoms (model 2), and (3) model 2 plus interaction between dLOC and sex (model 3). Sex-specific estimates were also obtained in stratified analyses for models 1 and 2. Analyses were completed in SAS 9.4.

Results

Participant Characteristics

Sample characteristics are presented in Table 1. Approximately half of the sample was male (49.0%) and participants of both sex were predominately white (86.0%; p=0.73). The average participant age overall was 67.2 ± 3.38 years at baseline and did not differ by sex. The overall sample was highly educated, with 29.84% reporting their highest educational attainment as a graduate or professional degree, and 32.83% reporting highest educational attainment as a bachelor’s degree. Males were slightly more educated with 34.3% reporting their highest level of educational attainment as a graduate or professional degree compared to 25.6% of females, while a slightly higher percentage of women (41.1%) reported highest educational attainment of some college or less compared to men (33.4%). Males were more likely to have experienced hypoglycemic episodes (81.1%) compared to females (72.3%),

while women were more likely to self-reported notable depressive feelings during their lifetime (38.1%) than men (23.7%).

Participants had an average dLOC of 7.4 representing a more internal locus of control, with a minimum observed score of −6 and a maximum score of 12 out of a possible range of −12 to 12. Distributions of dLOC responses are presented in Figure 1. Participants were likely to "agree" or "strongly agree" for all questions representing internal locus of control, with 93.9% agreeing with "Taking care of my diabetes is a high priority right now", 93.2% agreeing with "What I do has a big effect on my health", and 74.3% agreeing with "I can avoid complications of my diabetes". Conversely, participants were likely to "strongly disagree" or "disagree" for all questions representing external control, with 66.5% disagreeing with "I have many more important things in my life than diabetes right now", 91.8% disagreeing that "Good blood sugar is a matter of luck", and 84.1% disagreeing that "My blood sugars will be what they will be". Sex-specific component distributions differed slightly but did not lead to significant differences in the overall dLOC score.

Diabetes Locus of Control and Cognition

Initial regression models for each cognitive outcome adjusted for race, sex, and age are shown in Table 2. Results represent increases in standard deviations of cognition for each point increase in dLOC, where negative values of dLOC reflect external dLOC scores and positive values represent internal dLOC scores. In these minimally adjusted models (model 1), higher dLOC predicted increases in global cognition (β=0.04, 95% CI: 0.02-0.06), language (β=0.04, 95% CI: 0.02-0.06), and executive function (β=0.04, 95% CI: 0.02-0.06). No statistically significant association was observed between dLOC and episodic memory or attention, though effect estimates were trending in the same direction as global cognition, language, and executive functioning. Models further adjusting for age of diabetes diagnosis, education, lifetime hypoglycemic episodes, and self-reported lifetime depression showed similar associations (model 2), with each point increase in locus of control associated with an increase of 0.03 points in global cognition (β=0.03, 95% CI: 0.01, 0.05), language (β=0.03, 95% CI: 0.01, 0.05), and executive function (β=0.03, 95% CI: 0.01, 0.05). After assessing for potential effect modification by sex (model 3), interaction between dLOC and sex was found for global cognition (β=−0.04, 95% CI: −0.04, −0.00) and suggested for domain-specific cognitive outcomes, though did not reach statistical significance.

Sex Differences in the Relationship between Diabetes Locus of Control and Cognition

Results of sex-specific analyses are presented in Table 3. In stratified analyses, no relationship was found between changes in dLOC and any cognitive outcome in females, with no effect for global cognition (β=−0.00, 95% CI: −0.01, 0.01), language (β=0.00, 95% CI: −0.03-0.04), executive function (β=0.01, 95% CI: −0.02, 0.04), episodic memory (β=0.00, 95% CI: −0.03, 0.03), and attention (β=−0.01, 95% CI: −0.04, 0.01). In males, global cognition (β=0.05, 95% CI: 0.02, 0.08), language (β=0.05, 95% CI: 0.02, 0.08), and executive function (β=0.04, 95% CI: 0.02, 0.07), episodic memory (β=0.03, 95% CI: 0.00, 0.06), and attention (β=0.03, 95% CI: −0.01, 0.07) were associated with dLOC adjusting for all covariates although estimates for episodic memory and attention did not reach statistical significance.

Discussion

Diabetes locus of control was consistently more likely to be internal in both sexes with very few individuals reporting external locus of control of any magnitude. On average, men had lower average cognitive performance scores than women across all domains. Diabetes-related locus of control predicted cognition only in men and not women in this sample of older adults with type 1 diabetes mellitus. Consistent associations were seen for global cognition, language, and executive function but not for episodic memory or attention, with each point increase in locus of control corresponding to a change of 0.05 standard deviations of global cognition, 0.05 standard deviations of language, and 0.04 standard deviations of executive function. A participant with the minimum observed dLOC of −6 compared to a participant with the maximum observe dLOC of 12 would have a difference of approximately 0.90 standard deviations of global cognition, 0.72 standard deviations of language, and 0.72 standard deviations of executive functioning.

As few studies have examined adults with type 1 diabetes mellitus in later life, the mechanisms of how diabetes-related locus of control affects cognition in this population remain unclear. However, cognition is known to be influenced by aspects of psychological well-being and attitudes in non-diabetic individuals, with control beliefs found to couple with cognition.[19] One suggested mechanism between the relationship with dLOC and cognition is a relationship between dLOC and treatment adherence, treatment type, or metabolic control, though results are sometimes contradictory.[20,21] Health locus of control was associated with improved adherence to diabetes regimens among Iranian adults with type 1 or type 2 diabetes.[22] while a recent meta-analysis found no relationship between locus of control and metabolic control of diabetes.[23] Exposure to severe hypoglycemia or hyperglycemia, a result of poor metabolic control, may also explain part of the pathway between dLOC and cognition as a number of retrospective studies in adults with type 1 diabetes mellitus have found associations between history of severe hypoglycemia and severe cognitive impairment.[24] However, prospective studies and a subsequent meta-analysis found that compared with nondiabetic controls, individuals with type 1 diabetes mellitus showed significantly lowered cognitive performance that was associated with microvascular complications but not with poor metabolic control or severe hypoglycemic episodes.[25] Chronic hyperglycemia has also been shown to affected brain function and cognitive decline, though residual confounding by selective survival may be a concern.[26,27] Metabolic control measures may also act as confounding factors on the relationship between locus of control and cognition if acting as determinants of both locus of control and cognition, such as in the case that a person experiencing more frequent hypoglycemic episodes may subsequently feel as if their disease status is due to more external factors. Therefore, we addressed this by controlling for self-reported lifetime severe hypoglycemic episodes (those involving passing out or needing help to treat the reaction) as a temporally preceding experience to the measurement of our exposure and outcome.

The differing associations between dLOC and cognition in males and females presented in this study may be driven by differences in unmeasured health behaviors or dispositions to comorbidities across sexes. In recent years, life expectancy for individuals with type 1 diabetes mellitus has increased by approximately 2 years for men but not women, possibly

driven by reduced cardiovascular mortality in men overall[28] that may in turn affect cognition. Incidence rates for type 1 diabetes are higher for males between the ages of 15 to 39 but approximately equal in childhood and later life,[29,30] and it's possible the age of diagnosis for type 1 diabetes may have differential effects on health behaviors that modify the relationship between locus of control. However, though previous work has found similar inverse relationships between external locus of control and cognition in men and women, [11,12] these results were found in separate cohorts of different ages and additionally may differ from the individuals examined in later life with type 1 diabetes in our sample.

This study has strength as a prospectively collected cohort of elderly individuals with T1D with a large sample size and the ability to examine multiple cognitive domains. Limitations of this study includes the cross-sectional design, as it includes only baseline data from individuals with type I diabetes from the ongoing SOLID study. Data collection is ongoing, and future analyses will use longitudinal data and make comparisons with individuals with type 2 diabetes and non-diabetic controls and also explore the role of vascular comorbidities on cognition. Conclusions were limited as the directionality of the relationship could not be definitively established, and further research is needed to support the robustness of these findings and whether changes in either dLOC or cognition over time affect this relationship; for example, a large multisite randomized controlled trial found significant improvements in internal locus of control with cognitive training targeting reasoning and processing speed, suggesting a possible pathway in which cognition precedes locus of control.[31] Furthermore, our sample is subject to selective survival prior to study age eligibility and it is unknown whether this KPNC cohort is representative of older individuals with type 1 diabetes mellitus. This likely contributed to the sociodemographic composition of our sample, which was predominately white and highly educated. Selective survival may also explain the high internal locus of control and high levels of education observed throughout our sample. However, this study provides a basis for further investigations as the demographic of aging individuals with type 1 diabetes changes and overall life expectancy in this population rises. This study also does not collect neuroimaging or pathology data that could provide further information on possible etiologic characteristics driving the difference between sexes.

To our knowledge, this is the first study to highlight sex differences in the relationship between diabetes-related locus of control and cognitive function in older adults with type 1 diabetes mellitus. Locus of control serves as a potential intervenable characteristic as it has been shown to vary over short periods of time, such as from one week to the next,[12,19,32] and intervention studies have found both associations between locus of control and cognition as well as an intervention study examining locus of control and cognition in non-diabetic populations also found that some racial disparities persisting after memory and reasoning training are attributable to locus of control.[33,34] The findings of this study further suggest that modifications to diabetes locus of control may potentially affect cognitive function in later life, but that underlying differences are present among men and women even after adjusting for potentially confounding factors such as age at diabetes diagnosis. High levels of care are required for management of type 1 diabetes and are impacted by cognitive changes in later life, and future research is necessary to continue to explore possible protective factors or vulnerabilities in this increasingly aging population, as well as potential drivers of differential effects across domains of cognitive performance.

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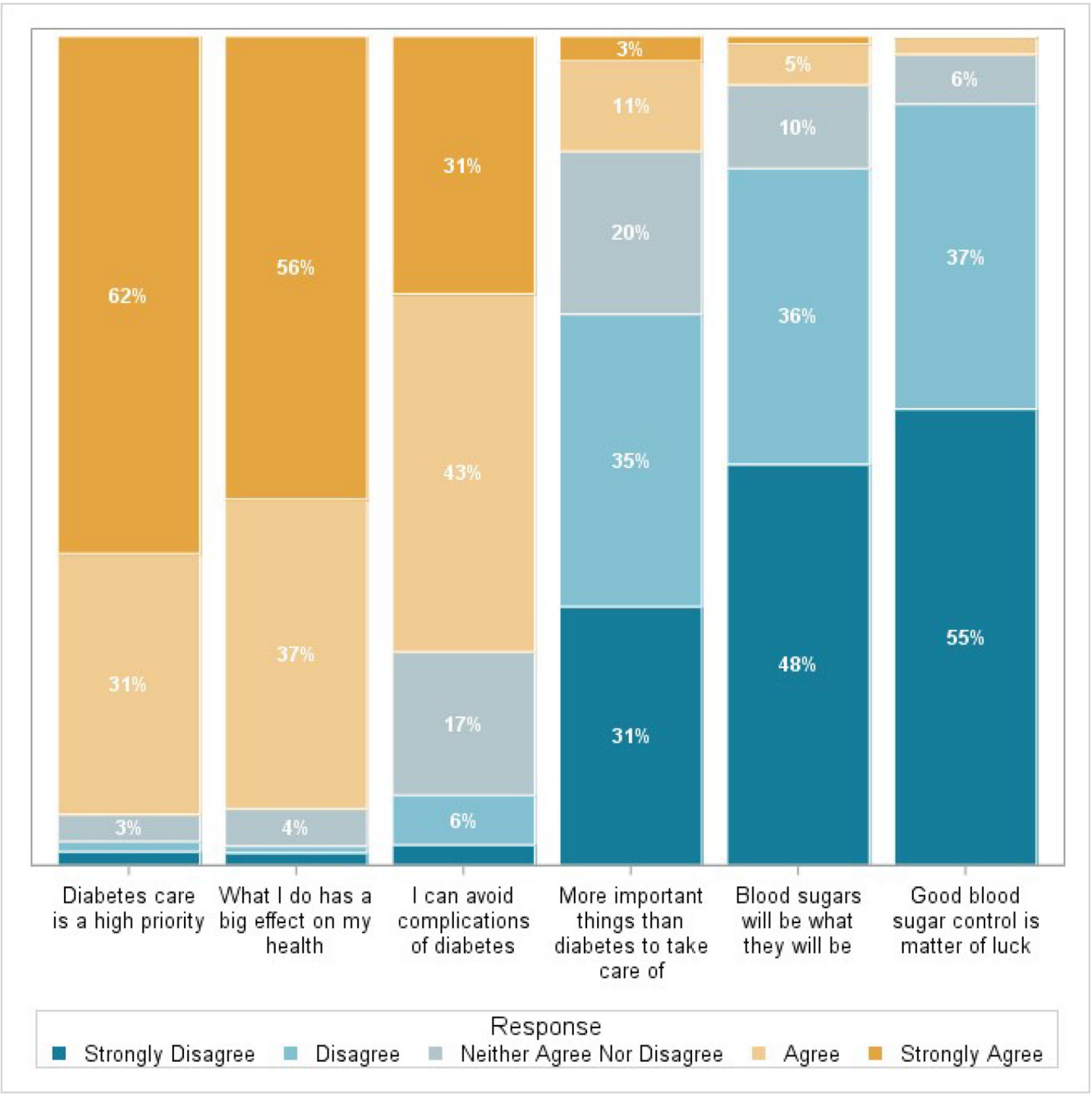

Figure 1.
Distribution of diabetes locus of control component responses.

Table 1.

Descriptive characteristics of SOLID participants with type 1 diabetes mellitus.

	Female (n=375)			Male (n=359)			Overall (n=734)			Sex Differences
	Mean / N	SD	PCT	Mean / N	SD	PCT	Mean / N	SD	PCT	p-value
Age at survey, mean (SD)	66.97	6.24		67.52	6.51		67.24	6.38		0.2477
Race [n (%)]										0.7301
White	324		86.40%	307		85.52%	631		85.97%	
Non-White	51		13.60%	52		14.48%	103		14.03%	
Highest level of educational attainment [n (%)]										
Some college or less	154		41.07%	120		33.43%	274		37.33%	0.0231
Bachelor's Degree	125		33.33%	116		32.31%	241		32.83%	
Graduate or Professional Degree	96		25.60%	123		34.26%	219		29.84%	
Age at diabetes diagnosis										0.0118
< 10 years	39		10.40%	21		5.85%	60		8.17%	
10 to 19 years	93		24.80%	100		27.86%	193		26.29%	
20 to 39 years	140		37.33%	162		45.13%	302		41.14%	
40 years or older	103		27.47%	76		21.17%	179		24.39%	
History of hypoglycemic episodes	271		72.27%	291		81.06%	562		76.57%	0.0161
Any lifetime depressive feelings	143		38.13%	85		23.68%	228		31.06%	<.0001
Cognition Factor Scores										
Global Cognition	0.13	0.53		−0.09	0.51		0.02	0.53		<.0001
Language	0.05	0.74		0.01	0.71		0.03	0.73		0. 4629
Executive Function	0.11	0.79		−0.06	0.78		0.03	0.79		0.0040
Memory	0.19	0.71		−0.15	0.69		0.02	0.72		<.0001
Attention	0.16	0.69		−0.14	0.89		0.01	0.81		<.0001
Diabetes Locus of Control										
Mean Score	7.24	3.04		7.62	3.21		7.42	3.13		0.0989

Table 2.

Association between Locus of Diabetes Control and Cognition Factor Scores (N=734)

		Model 1			***Model 2***			***Model 3***		
		Minimal Adjustment (race, sex, age)			***Additional Adjustments (diagnosis age, education, hypotensive episodes, depression)***			***Full adjustment + interaction between LOC and Sex***		
		Effect Estimate	**95% CI**		**Effect Estimate**	**95% CI**		**Effect Estimate**	**95% CI**	
			Lower	**Upper**		**Lower**	**Upper**		**Lower**	**Upper**
Model Outcome	Exposure									
Global cognition	dLOC	**0.04**	**0.02**	**0.06**	**0.03**	**0.01**	**0.05**	**0.05**	**0.02**	**0.07**
	Sex	**0.39**	**0.26**	**0.51**	**0.44**	**0.32**	**0.57**	**0.74**	**0.43**	**1.06**
	Sex x dLOC							**−0.04**	**−0.08**	**−0.00**
Language	dLOC	**0.04**	**0.02**	**0.06**	**0.03**	**0.01**	**0.05**	**0.04**	**0.01**	**0.07**
	Sex	0.03	−0.11	0.16	0.08	−0.05	0.21	0.32	−0.01	0.66
	Sex x dLOC							−0.03	−0.07	0.01
Executive function	dLOC	**0.04**	**0.02**	**0.06**	**0.03**	**0.01**	**0.05**	**0.04**	**0.01**	**0.07**
	Sex	**0.16**	**0.02**	**0.29**	**0.21**	**0.07**	**0.34**	**0.43**	**0.10**	**0.76**
	Sex x dLOC							−0.03	−0.07	0.01
Episodic Memory	dLOC	0.02	0.00	0.04	0.01	−0.01	0.03	0.02	−0.01	0.05
	Sex	**0.49**	**0.36**	**0.63**	**0.52**	**0.39**	**0.66**	**0.67**	**0.33**	**1.00**
	Sex x dLOC							−0.02	−0.06	0.02
Attention	dLOC	0.01	−0.01	0.03	0.01	−0.01	0.03	0.03	−0.01	0.06
	Sex	**0.37**	**0.22**	**0.51**	**0.40**	**0.25**	**0.54**	**0.64**	**0.27**	**1.02**
	Sex x dLOC							−0.03	−0.08	0.01

*Referent sex category is male. Referent age of diagnosis category is <10 years. Referent education category is some college or less.

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Table 3.

Fully adjusted associations between diabetes-specific locus of control and cognitive factor scores, stratified by sex (n=734)

	Female			***Male***		
	Effect Estimate	**95% CI**		**Effect Estimate**	**95% CI**	
		Lower	**Upper**		**Lower**	**Upper**
Model Outcome						
Global cognition	−0.00	−0.03	0.03	**0.05**	**0.02**	**0.08**
Language	0.00	−0.03	0.04	**0.05**	**0.02**	**0.08**
Executive function	0.01	−0.02	0.04	**0.04**	**0.02**	**0.07**
Episodic Memory	0.00	−0.03	0.03	0.03	0.00	0.06
Attention	−0.01	−0.04	0.01	0.03	−0.01	0.07