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Insulin-like growth factor-1 and cognition in normoglycemia, prediabetes, and type 2 diabetes mellitus

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ABSTRACT

Background: The relationship between insulin-like growth factor-1 (IGF-1) and cognition has been studied in healthy individuals, but not extensively with regards to insulin resistance and type 2 diabetes mellitus (T2DM). In this retrospective observational study, we investigated relationships of IGF-1 with memory and executive function across people with normoglycemia, prediabetes, and T2DM.

Methods: Data from the Midlife in the United States (MIDUS) study were used. Episodic memory and executive function were assessed using the Brief Test of Adult Cognition by Telephone approximately 21.42 ± 12.10 months prior to measuring IGF-1 levels from a fasting blood sample. Normoglycemia was identified as individuals without a physician diagnosis of diabetes and glycated hemoglobin (HbA1c) ≤5.6%. Prediabetes was identified as those without a physician diagnosis of diabetes and HbA1c between 5.7%−6.4%. T2DM was identified as anyone with a physician diagnosis of diabetes, or HbA1c ≥6.5%, or anyone using an oral hypoglycemic medication. The associations were assessed using linear regressions controlling for age, sex, education, body mass index, C-reactive protein, HbA1c or homeostatic model of insulin resistance, MIDUS wave, exercise, smoking status, sleep quality, alcohol intake, oral hypoglycemic use, and insulin use.

Results: The study included 1400 participants, which consisted of 583 normoglycemic (48.4% female, mean age 51.0 ± 12.2 years), 512 prediabetes (58.4% female, mean age 57.3 ± 11.8 years), and 305 T2DM participants (53.8% female, mean age 57.6 ± 11.5 years). Peripheral IGF-1 concentrations were lower ($F_{2,1397} = 28.29$, $p < 0.001$) in people with prediabetes or T2DM, vs. normoglycemia. Participants with prediabetes or T2DM had lower episodic memory ($F_{2,1397} = 9.21$, $p < 0.001$) and executive function ($F_{2,1397} = 20.29$, $p < 0.001$) composite z-scores than people with normoglycemia. Higher IGF-1 concentrations were associated with better executive performance in individuals with prediabetes ($\beta = 0.115$ [0.028, 0.202], $p = 0.010$), but not in individuals with normoglycemia or T2DM. An interaction between IGF-1 and sex in predicting executive function was observed in the prediabetes group ($\beta = -0.344$, $p = 0.042$), where the relationship was weaker in females ($\beta = 0.106$ [−0.012, 0.224], $p = 0.077$) than males ($\beta = 0.251$ [0.123, 0.380], $p < 0.001$). No associations were seen between IGF-1 and memory.

Conclusion: The results suggest that peripheral IGF-1 concentrations may be related to executive function, and that the relationship may be sex-specific and dependent on diabetes status.

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1. Introduction

People with type 2 diabetes mellitus (T2DM) often experience accelerated cognitive decline and are at increased risk for mild cognitive impairment (MCI) and dementia (Yuan and Wang, 2017). Cognitive impairment can negatively impact the quality of life and diabetes management (Munshi et al., 2006), and impose a substantial burden on the health care system (Wimo et al., 2013). Despite the advances in understanding the causes of T2DM-related cognitive impairment (Gaspar et al., 2016), the breadth of associated neuroendocrine changes is not fully understood. A decline in insulin-like growth factor-1 (IGF-1) signaling may be one potential mechanism (Frater et al., 2018; Gaspar et al., 2016).

IGF-1 is an anabolic hormone involved in growth, development, and aging (Frater et al., 2018). Approximately 75% of circulating IGF-1 is produced by the liver through the growth hormone/IGF-1 axis, which is stimulated by the release of growth hormone releasing hormone (GHRH) from the hypothalamus (Frater et al., 2018). IGF-1 can also be produced locally in the brain or be transported into the brain from the periphery through transcytosis by binding to the IGF-1 receptor or the low-density lipoprotein receptor-related protein 2 (Ashpole et al., 2015). IGF-1 receptors are expressed in many different types of cells, including neurons, astrocytes, and endothelial cells, and they are involved in neurogenesis, angiogenesis, and neuroprotection (Torres-Aleman, 2010). In animal studies, complete knockout of IGF-1 signaling often resulted in lethality (Ashpole et al., 2015). Animal and human studies have shown that genetic mutations in IGF-1 and/or the IGF-1 receptor resulted in microcephaly and central nervous system hypomyelination (Ashpole et al., 2015).

Due to its important role in the central nervous system, IGF-1 has been studied in the context of cognition in samples of predominantly healthy individuals, but the results have been inconclusive. For instance, cross-sectional observational studies showed that higher IGF-1 levels were associated with better general cognitive performance and verbal fluency in healthy, older men (Al-Delaimy et al., 2009). Similar results have also been reported by other studies comparing healthy participants and those with MCI (Doi et al., 2015), or in healthy males (Aleman et al., 1999). However, some studies reported the opposite association in females older than 95 years of age (Perice et al., 2016), or no cross-sectional association between IGF-1 and general cognitive performance in a healthy, midlife, Caucasian population (Licht et al., 2014), and in older males (Tumati et al., 2016).

Many studies investigating the association between IGF-1 and cognition did not characterize their populations with respect to diabetes status, or they excluded individuals with T2DM (Doi et al., 2015; Licht et al., 2014). Considering that insulin signaling can affect IGF-1 levels (Clemmons, 2012), and that individuals with T2DM are at increased risk of cognitive impairment, it is worth investigating the association between IGF-1 and cognition with particular attention to diabetes status (Yuan and Wang, 2017). Among the few studies that investigated this relationship, a positive association was found between IGF-1 and cognitive performance in individuals with T2DM with or without MCI (Rui-Hua et al., 2019). Another study did not find a significant difference in IGF-1 levels in individuals with T2DM with or without MCI (Huang et al., 2015).

Impairments in memory and executive function are commonly observed in both T2DM and aging, and these processes are thought to be accelerated in Alzheimer's disease (Gaspar et al., 2016; Grober et al., 2008). Episodic memory entails abilities such as encoding, storing, and retrieving information, and executive function refers to a combination of abilities such as planning, organizing, and inhibition, to allow a goal-directed behavior (Cacciaglia et al., 2018). Although memory and executive function are closely related, as these domains are primarily affected by different neuroanatomical regions (Cacciaglia et al., 2018), and cognitive decline in T2DM can begin at the stage of prediabetes (MacIntosh et al., 2019), we aimed to investigate the relationship between IGF-1 and episodic memory or executive performance in individuals with normoglycemia, prediabetes, and T2DM. We hypothesized that relationships would be apparent between IGF-1 and episodic memory and executive function in people with prediabetes or T2DM. Because some studies have suggested sex differences in the relationship between IGF-1 and cognition (Al-Delaimy et al., 2009; Perice et al., 2016; Wennberg et al., 2018), we investigated the interaction with sex, and we examined associations in males and females separately.

2. Materials and methods

2.1. Participants

Data from the Midlife in the United States (MIDUS) study was used for retrospective analysis. The first wave of the MIDUS study began in 1995 to determine the impact of psychological, behavioral, and social factors on health and aging in a national sample of middle-aged Americans (Radler, 2014). English-speaking, noninstitutionalized participants were recruited by dialing random phone numbers. Participants from the first wave were followed-up in the second wave (2004–2009), and new participants were recruited in the refresher wave (2011–2016). The current study used the biomarker and cognitive data from participants in the second wave and the refresher wave of the MIDUS study. The first wave of MIDUS was not included, as measures of cognitive performance and biomarkers were introduced from the second wave and onwards.

For the present study, we excluded individuals with (1) missing IGF-1 or glycated hemoglobin (HbA1c) measures; (2) missing and/or invalid cognitive measures; (3) physiologically improbable homeostatic model of insulin resistance (HOMA-IR), defined as HOMA-IR >100; (4) self-reported cancer diagnosis; (5) self-reported medication use for epilepsy, Alzheimer's disease, or schizophrenia; and (6) self-reported use of insulin without concomitant use of oral hypoglycemics. Invalid cognitive measures were defined as having an invalid Stop and Go Switch Task (SGST) result due to one of the following: (1) technical malfunction, (2) distraction by external events, or (3) less than 75% accuracy on the test. These filters were suggested by the MIDUS researchers to ensure the SGST test was being performed accurately (Ryff and Lachman, 2021, 2023). In this study, we selected the normoglycemia group as individuals without a physician diagnosis of diabetes and HbA1c ≤5.6%. The prediabetes group was selected based on individuals without a physician diagnosis of diabetes and HbA1c between 5.7%−6.4%. The T2DM group was selected as anyone with a physician diagnosis of diabetes, or HbA1c ≥6.5%, or use of oral hypoglycemic medication. The cutoff values for HbA1c were based on the guidelines recommended by the American Diabetes Association (American Diabetes Association, 2010).

2.2. Measures

2.2.1. Cognition

In both waves of the MIDUS study, cognitive performance was assessed using the Brief Test of Adult Cognition by Telephone (BTACT) (Tun and Lachman, 2006). The BTACT consists of six cognitive tests: 1) Word list recall, where 15 words are read to the participants once and they are asked to recall the words immediately and following a delay (Lezak, 1995); 2) The Digits Backward test, where a string of digits of increasing length are read to the participants and they are asked to repeat them in reverse order (Wechsler, 1997); 3) The Category Fluency test, where the participants are asked to generate as many words belonging to a specific category as they can in a minute (Drachman and Leavitt, 1972); 4) The Number series test, where a series of numbers are read to the participants and they are asked to predict the next number (Salthouse and Prill, 1987); 5) The Backward Counting test, where the participants are asked to count backwards from 100 as fast as possible in half a minute (Kanno et al., 2012); and 6) The SGST, where participants

are first asked to respond to the word "red" with "stop", and "green" with "go", as fast as possible, and then the reverse, "red" with "go", and "green" with "stop", as fast as possible (Huizinga and van der Molen, 2011; Tun and Lachman, 2006).

The MIDUS study conducted an exploratory and confirmatory factor analysis of the BTACT measures, yielding two factors labeled as episodic memory and executive function (Lachman et al., 2014). Composite z-scores were created for each factor using the mean of the z-scores of individual tests, and then standardized with a mean of zero and a standard deviation of one. Episodic memory z-scores were calculated from the mean z-scores from immediate and delayed word list recall, and executive function z-scores was calculated from the mean z-scores from the digits backwards, category fluency, number series, backward counting, and SGST (Lachman et al., 2014). The composite z-scores were used as the main outcomes in this study.

2.2.2. Biomarkers

After an average of 21.42 ± 12.10 months from the phone interview during which cognitive assessments were administered, individuals who agreed to participate in the MIDUS biomarker study were asked to attend an in-person assessment at one of the three general clinical research centers: the University of Wisconsin-Madison, Georgetown University, or the University of California, Los Angeles, for a 24-hour stay. On the second day of the visit, fasting blood samples were collected, then processed and stored at − 60 °C to − 80 °C until shipped to the MIDUS Biocore lab for analysis. Informed consent was obtained from all participants, and the procedure for data collection was approved by the institutional review boards at each of the research centers.

Total IGF-1 levels were quantified from a fasting blood sample using an immunochemiluminescent assay on a Siemens Immulite® 2000 analyzer (assay range 25–1600 ng/mL) for the second wave, and on a DiaSorin Liaison® XL (assay range 10–1200 ng/mL) for the refresher wave (Ryff and Lachman, 2021, 2023). Both analyzers have been validated and commonly used to quantify IGF-1 levels (Elmlinger et al., 2004; Chanson et al., 2016). Other covariates such as HbA1c, C-reactive protein (CRP), insulin, and glucose levels, were also quantified from the fasting blood samples. HOMA-IR was calculated from fasting insulin and glucose levels using the following formula:

$$\frac{\text{Fasting } \textit{Glucose}\ (\text{mg/dL}) \times \text{Fasting Insulin}\ (\mu\text{IU/mL})}{405}$$

(Placzkowska et al., 2019). Higher HOMA-IR values indicate greater insulin resistance.

2.2.3. Other covariates

Demographic information such as sex and highest educational attainment were collected during the phone interview. Education was coded as a categorical variable with the following levels: less or equal to high school, college or bachelor's degree, or graduate school or above. During the in-person visit at the general clinical research centers for biomarker collection, participants also underwent a physical examination to collect information regarding their weight and height, from which body-mass index (BMI) was calculated. The participants were also asked to provide any information regarding previous medical history and medication use. Furthermore, they completed the Pittsburgh Sleep Quality Inventory (PSQI) to measure sleep quality (range 0–21), where a higher score on the PSQI indicates worse sleep quality (Buysse et al., 1989); the Global Physical Activity Questionnaire (GPAQ) to measure exercise levels in a typical week in total metabolic equivalents (MET), where greater MET/week indicates greater physical activity (Armstrong and Bull, 2006); and questionnaires to determine smoking history and alcohol intake in the past month. Smoking was dichotomized into not smoking and currently smoking.

2.3. Statistical analyses

All analyses were conducted using R version 4.1.0 (R Core Team, 2021). Multiple linear regression was used to determine the association between IGF-1 and episodic memory z-score or executive function z-score across the subgroups while controlling for important confounders. Potential confounders to the relationship between IGF-1 and cognition were determined a priori, which include age, sex, BMI, education, CRP, HbA1c or HOMA-IR, MIDUS wave, exercise, smoking status, sleep quality, alcohol intake, oral hypoglycemic use, and insulin use.

HbA1c was included in the model for whole group analyses, and HOMA-IR was included in the models for the subgroup analyses to account for the influence of insulin resistance within different diabetes status. CRP was included in the model, as inflammation is known to affect both IGF-1 levels and cognitive performance (Labandeira-Garcia et al., 2017; Noble et al., 2010). HOMA-IR, hypoglycemic medication, and insulin use were also included in the model, as previous studies have shown that insulin and oral hypoglycemic drugs can alter IGF-1 levels (Calle and Kaaks, 2004; Yang et al., 2020). The model also controlled for MIDUS wave to adjust for any differences between cognitive z-scores that were calculated separately within each wave (MIDUS 2 vs. MIDUS Refresher), and the different analyzers used to quantify IGF-1 across each wave. Exercise and smoking status were included in the model as they may influence peripheral IGF-1 levels (Cotman et al., 2007; Kapoor and Jones, 2005). Sleep quality and alcohol intake were controlled for in this study, as they can affect the growth hormone/IGF-1 axis or the liver to alter the production of IGF-1 (Chennaoui et al., 2020; Röjdmark et al., 2000). As previous studies have reported sex differences in the association between IGF-1 and cognitive outcomes, an interaction term for IGF-1 ×sex was added to the models to test for potential modifying effects by sex (Al-Delaimy et al., 2009; Wennberg et al., 2018).

Missing covariates were assumed to be missing at random or missing completely at random, and were imputed using the "mice" package in R (van Buuren and Groothuis-Oudshoorn, 2011). All variables in the model, as well as total score on the Center for Epidemiologic Studies Depression Scale (CES-D), cardiovascular disease diagnosis, hypertension diagnosis, total cholesterol, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and use of anti-inflammatory medication were used as predictors to impute education (n = 141 (10.1%)), CRP (n = 3 (0.2%)), exercise (n = 4 (0.3%)), smoking status (n = 1 (0.1%)), and sleep quality (n = 91 (6.5%)) data. Results from 10 imputations, each with 10 iterations, were pooled using Rubin's rules (Rubin, 2009). Variables were log-transformed prior to analyzes if they were not normally distributed. A sensitivity analysis was run with the complete dataset after excluding individuals with missing covariate data. Plots were created using the "ggplot2" package (Wickham, 2016).

3. Results

3.1. Participant characteristics

A total of 2118 participants completed both cognitive assessments and biomarker measurements. After applying the exclusion criteria, 1400 participants were included in the analyses (844 from MIDUS 2, 556 from MIDUS Refresher), of which 583 participants were defined as having normoglycemia, 512 participants with prediabetes, and 305 participants with T2DM (Fig. 1). The demographical and clinical characteristics of the participants are summarized in Table 1. Participant characteristics were compared between each subgroup. Peripheral IGF-1 concentrations in participants with prediabetes or T2DM were significantly lower than participants with normoglycemia ($F_{2,1397} = 28.29$, $p < 0.001$). Participants with prediabetes or T2DM also had lower episodic memory ($F_{2,1397} = 9.21$, $p < 0.001$) and executive function ($F_{2,1397} = 20.29$, $p < 0.001$) composite z-scores compared to individuals with normoglycemia. Participants with prediabetes and T2DM were older than participants with normoglycemia ($F_{2,1397} = 48.54$,

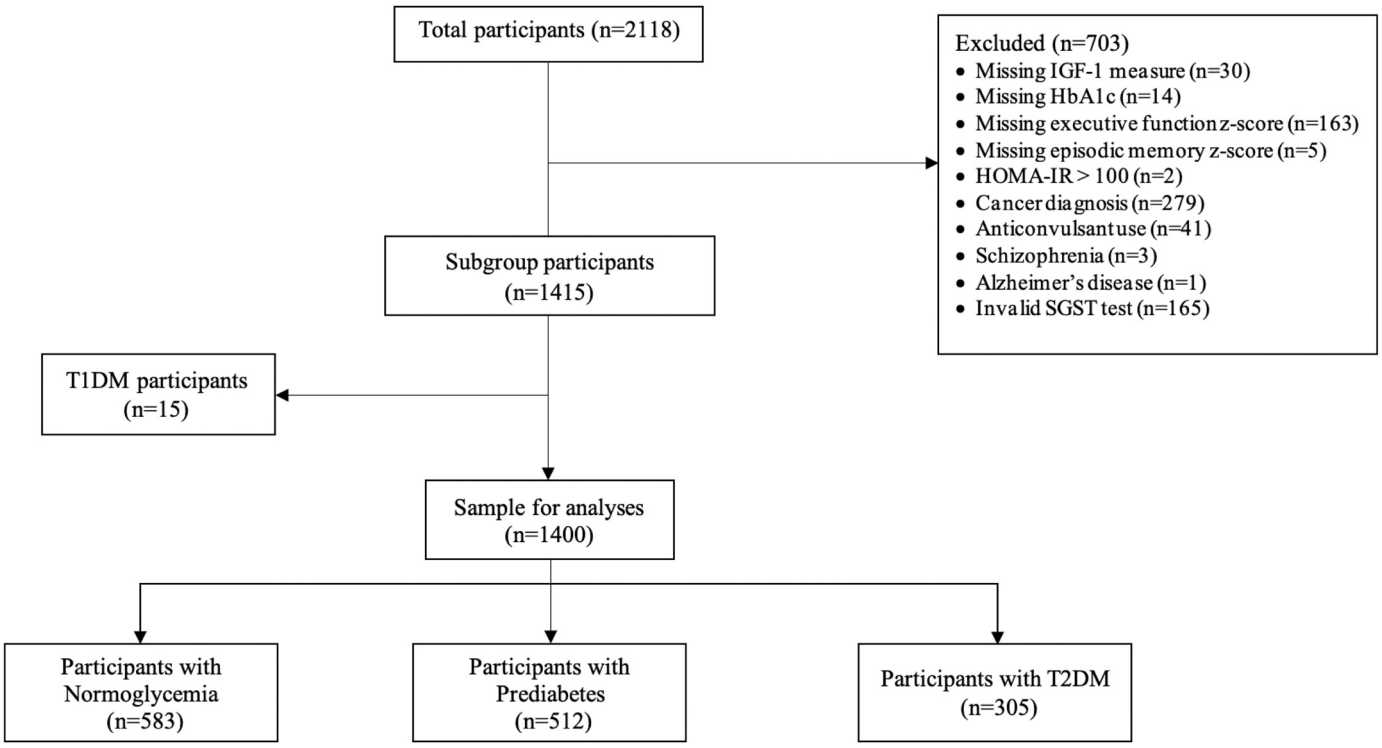

Fig. 1. Flow diagram of the MIDUS study illustrating the number of participants excluded due to each criterion. Abbreviations: IGF-1 = Insulin-like growth factor-1; HbA1c = glycated hemoglobin A1c; HOMA-IR = Homeostatic model of insulin resistance; T1DM = Type 1 diabetes mellitus; SGST = Stop and Go Switch Task; T2DM = Type 2 diabetes mellitus.

$p < 0.001$), had greater BMI ($\chi^2 = 67.87$, $p < 0.001$) and CRP levels ($F_{2,1397} = 21.76$, $p < 0.001$). Additionally, compared to the normoglycemic subgroup, individuals with T2DM also had lower daily physical activity ($F_{2,1397} = 4.21$, $p = 0.015$), and worse sleep quality ($F_{2,1397} = 6.22$, $p = 0.002$), compared to those with normoglycemia.

3.2. Associations between IGF-1 and episodic memory

In the whole group, when adjusting for important confounders, no association was observed between IGF-1 and episodic memory ($\beta = 0.002$ [−0.052, 0.057], $p = 0.928$; Fig. 2**A**). When stratified into subgroups, no significant associations were observed in individuals with normoglycemia ($\beta = -0.001$ [−0.084, 0.082], $p = 0.985$; Fig. 2**B**), prediabetes ($\beta = 0.010$ [−0.077, 0.098] $p = 0.819$; Fig. 2**C**), or T2DM ($\beta = -0.035$ [−0.152, 0.081], $p = 0.550$; Fig. 2**D**). No interactions between IGF-1 and sex were observed in the whole sample, or within subgroups.

3.3. Associations between IGF-1 and executive function

When adjusting for important confounders, no association was observed between IGF-1 and executive function in the whole group ($\beta = 0.042$ [−0.011, 0.095], $p = 0.117$; Fig. 3**A**). When stratified into subgroups, no associations were observed between IGF-1 and executive function in individuals with normoglycemia ($\beta = 0.053$ [−0.030, 0.135], $p = 0.209$; Fig. 3**B**). However, in individuals with prediabetes, higher IGF-1 levels were associated with better executive function ($\beta = 0.115$ [0.028, 0.202], $p = 0.010$; Fig. 3**C**). No association was observed in the T2DM group ($\beta = -0.092$ [−0.203, 0.018], $p = 0.101$; Fig. 3**D**). An interaction effect between IGF-1 and sex was observed in individuals with prediabetes ($\beta = -0.344$ [−0.676, −0.013], $p = 0.042$), such that the positive association between IGF-1 and executive function was slightly weaker in females ($\beta = 0.106$ [−0.012, 0.224], $p = 0.077$) than in males ($\beta = 0.251$ [0.123, 0.380], $p < 0.001$). No sex interaction was observed in the whole group, normoglycemic subgroup, or the T2DM subgroup. Though no significant interaction effect between IGF-1 and sex was observed in T2DM, a negative borderline association was present in males ($\beta = -0.158$ [−0.328, 0.011], $p = 0.067$), yet not in females ($\beta = -0.004$ [−0.162, 0.153], $p = 0.956$).

3.4. Sensitivity analyses

As some covariates were imputed in some individuals, all analyses were repeated using the complete dataset. The demographic and clinical characteristics in each subgroup after excluding participants with missing covariates are summarized in Supplementary Table 1. When investigating the association between IGF-1 and cognitive measures with the complete data, the results were generally consistent with the imputed dataset. No associations between IGF-1 and episodic memory were observed in the whole sample, or in the subgroup with normoglycemia, prediabetes, or T2DM. When comparing the association between IGF-1 and executive function, no association was observed in the whole sample, or in individuals with normoglycemia or T2DM. However, in individuals with prediabetes, a positive association between IGF-1 and executive function was present, and this association was stronger in males (see Supplementary Results 1.1). A negative borderline association between IGF-1 and executive function was observed in males with T2DM, opposite to what is observed in males with prediabetes.

As IGF-1 concentrations can be influenced by insulin, the association between IGF-1 and episodic memory or executive function in the T2DM group was repeated excluding individuals using insulin ($n = 19$). The results were generally consistent with the original analysis, where no association was observed between peripheral IGF-1 levels and memory performance, and a borderline, negative association was present with executive performance, particularly in males (see Supplementary Results 1.2).

Table 1
Participant demographics and clinical characteristics in subgroups with normoglycemia, prediabetes and T2DM.

	Normoglycemia (n = 583)	Prediabetes (n = 512)	T2DM (n = 305)	F/χ2	p-value
Female, n(%)	282 (48.4%)	299 (58.4%)	164 (53.8%)	11.06	**<0.001**
Age (years)	51.0 ± 12.2	57.3 ± 11.8	57.6 ± 11.5	48.54	**<0.001**
Education, n(%)	89 (15.3%)	128 (24.9%)	84 (27.6%)	11.12[a,b]	**<0.001**
High school or less	320 (54.9%)	266 (52.0%)	155 (50.9%)		
Some college or Bachelor's	174 (29.8%)	118 (23.1%)	65 (21.5%)		
Graduate degree or higher					
Ethnicity, n(%)	490 (84.0%)	408 (79.7%)	219 (71.8%)	17.01[c]	**<0.001**
Caucasian	46 (7.9%)	75 (14.6%)	62 (20.3%)		
Black	10 (1.7%)	5 (1.0%)	9 (3.0%)		
Native American	7 (1.2%)	3 (0.6%)	3 (1.0%)		
Asian	1 (0.2%)	0 (0.0%)	0 (0.0%)		
Native Hawaiian	28 (4.8%)	20 (3.9%)	9 (3.0%)		
Other	1 (0.2%)	1 (0.2%)	3 (1.0%)		
Missing					
BMI (kg/m^2)	27.2 (23.7-30.7)	28.9 (25.2-32.6)	30.7 (25.8-35.6)	67.87[d]	**<0.001**
CRP (μg/mL)	0.97 (0.01-1.94)	1.35 (0.68-2.02)	2.02 (0.28-3.77)	21.76[e]	**<0.001**
HOMA-IR	2.1 (1.1-3.2)	2.5 (1.2-3.9)	3.9 (1.4-6.4)	98.47[e]	**<0.001**
HbA1c (%)	5.4 (5.2-5.6)	5.9 (5.7-6.1)	6.5 (5.8-7.2)	935.79[d]	**<0.001**
Exercise (Total MET/week)	1039 (172-1907)	825 (0-1753)	540 (0-1182)	4.21	**0.015**
Smoking, n(%)	57 (9.8%)	60 (11.7%)	33 (10.8%)	0.57[b]	0.567
Sleep quality	5.0 (2.7-7.3)	5.0 (2.5-7.5)	6.0 (4.0-8.0)	6.22	**0.002**
Alcohol intake (# of drinks/month)	6.6 (0.0-19.7)	1.5 (0.0-8.2)	1.5 (0.0-9.3)	51.35[d]	**<0.001**
Oral hypoglycemic use, n(%)	N/A	N/A	102 (33.4%)	N/A	N/A
Insulin use, n(%)	N/A	N/A	19 (6.2%)	N/A	N/A
Episodic Memory (z-score)	0.24 ± 0.94	0.10 ± 0.90	-0.03 ± 0.91	9.21	**<0.001**
Executive Function (z-score)	0.43 ± 0.86	0.17 ± 0.91	0.06 ± 0.93	20.29	**<0.001**

Note: Demographic and clinical characteristics are summarized as mean ± SD or median (IQR) based on the distribution. Continuous variables were compared using one-way ANOVA or Kruskal-Wallis test, and categorical variables were compared using chi-square tests. For variables that were imputed, the tests were conducted separately in each imputation dataset, and then pooled using Rubin's rules.
Abbreviations: T2DM = Type 2 diabetes mellitus; BMI = Body mass index; CRP = C-reactive protein; HOMA-IR = Homeostatic model of insulin resistance; MET = Metabolic equivalent
*Higher values of HOMA-IR indicate greater insulin resistance.
*Higher total MET/week indicates greater physical activity in a typical week.
[a] Chi-square test with 2 degrees of freedom was conducted (High school or less vs. college or higher)
[b] F-statistic is reported instead of χ2 due to pooling from multiple imputation
[c] Chi-square test with 2 degree of freedom was conducted (Caucasian vs. other). Statistics were conducted on participants who reported their ethnicity (n = 1395)
[d] Kruskal-Wallis test was conducted as the equal variance assumption was violated
[e] Variables were log transformed prior to comparison

To preserve statistical power for each cognitive measure, the main analyses were repeated using pairwise deletion for each composite z-scores. Consistent to the main analyses, no associations between IGF-1 and episodic memory were observed in the whole sample, or across subgroups. Greater IGF-1 levels were associated with better executive performance only in individuals with prediabetes, and this positive association was stronger in males than females (see Supplementary Results 1.3).

4. Discussion

The current study investigated the association between IGF-1 and cognition in individuals with normoglycemia, prediabetes, and T2DM. To the best of our knowledge, no other study has compared the relationship between IGF-1 and cognition across groups differentiated by their diabetes status. Though no associations were found between IGF-1 and episodic memory in any of the subgroups, higher IGF-1 levels were associated with better executive performance in individuals with prediabetes.

In the present study, several clinical differences were observed across the subgroups, particularly with regards to CRP, exercise, and sleep quality. Despite the differences between the subgroups, these characteristics did not significantly predict cognitive measures in the whole group, or subgroup analyses.

The relationship between IGF-1 and executive function in people with prediabetes supported our hypotheses. Although particular mechanisms cannot be inferred, IGF-1 is known to have many effects on the cerebral vasculature, related to angiogenesis (Torres-Aleman, 2010) and the regulation of cerebral blood flow (Toth et al., 2015). Accordingly, studies investigating the changes in brain magnetic resonance imaging (MRI) with plasma IGF-1 concentrations reported a negative association between IGF-1 and white matter hyperintensities (WMH), a marker of cerebral small vessel disease (Wittfeld et al., 2022), and a positive association between IGF-1 and blood flow in middle cerebral arteries (Toth et al., 2022). As damage to the cerebral small vessels can result in executive dysfunction, it is possible that peripheral IGF-1 might have been related to executive function via vascular effects (O'Sullivan et al., 2005). Future studies might further explore these potential mechanisms.

The lack of association between IGF-1 and episodic memory did not support our hypotheses, since IGF-1 is known to be involved in adult neurogenesis and its receptors are highly expressed in the hippocampus, a region important for learning and memory (Frater et al., 2018). The reason for the lack of association is unclear. However, it is possible that the memory measure from the BTACT was less reliable or sensitive than the executive measure. Although the BTACT used tests derived from the Rey Auditory Verbal Learning Test (RAVLT) to measure memory performance, it was modified such that the participants only heard the list of words once, instead of five times as in the original test (Bean, 2011).

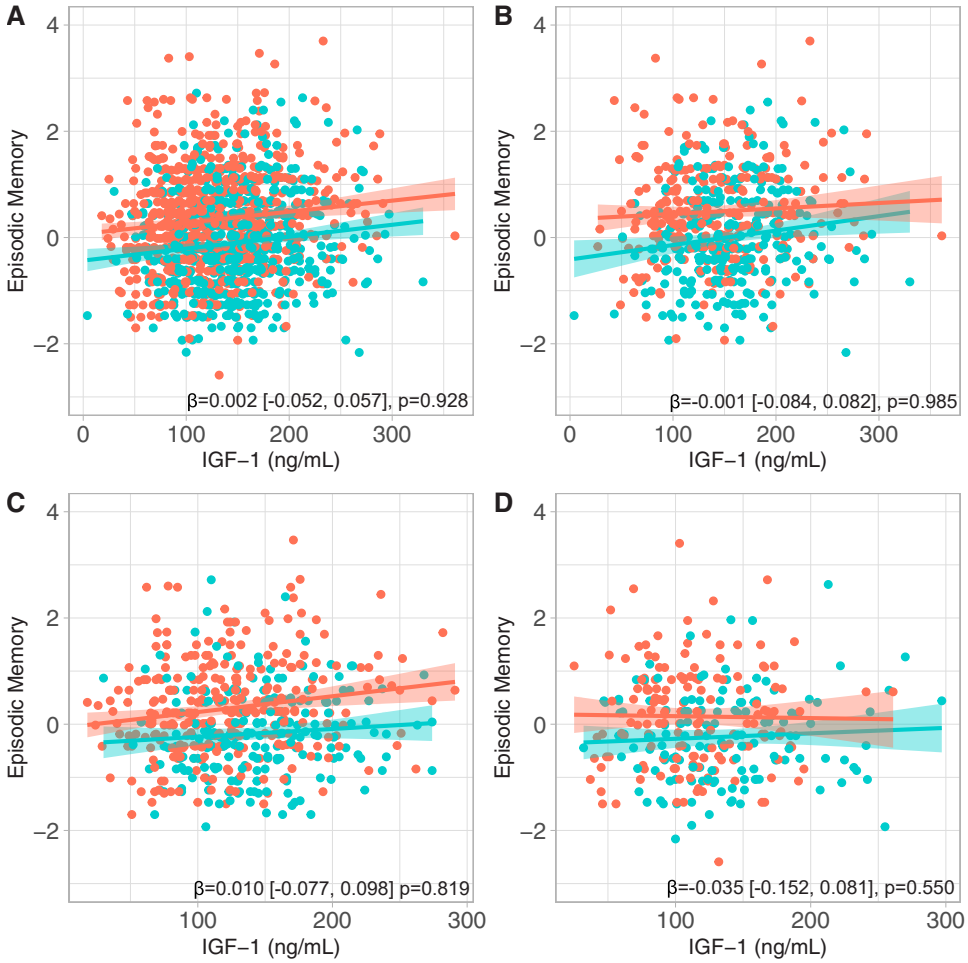

Fig. 2. Associations between IGF-1 and episodic memory z-score in (A) the whole sample, (B) normoglycemia, (C) prediabetes, and (D) T2DM. Males are represented in blue, and females are represented in red.

Therefore, the learning process may not have been established sufficiently to measure memory performance.

In the normoglycemia group, there were no association between IGF-1 and episodic memory or executive function. The present results in normoglycemic individuals were consistent with a study by Licht and colleagues, wherein the authors found no relationship between a functional IGF-1 polymorphism and cognitive performance in a healthy, middle-aged (mean age 42.4 years) Caucasian population, despite differences in peripheral IGF-1 concentrations across homozygotic, heterozygotic, and non-carriers of the 192 bp allele (Licht et al., 2014). Earlier findings found positive associations in populations (Al-Delaimy et al., 2009; Doi et al., 2015). The study by Doi and colleagues compared IGF-1 levels in cognitively normal individuals and those with MCI and found that individuals in the lowest IGF-1 quartile were more likely to have MCI (Doi et al., 2015). In the MIDUS study we were unable to determine the proportion of individuals who were cognitively normal versus those with MCI, which may have contributed to the different findings. In another study, higher IGF-1 levels were associated with better scores on the Mini-Mental State Exam and verbal fluency tests in men (Al-Delaimy et al., 2009), whereas in the current study, even when stratified by sex, no association was observed between IGF-1 and cognitive measures in participants with normoglycemia. However, both of those studies did not consider glycemic status or the use of antidiabetic medication, which may influence IGF-1 levels (Yang et al., 2020). Additionally, the mean age in both studies were much older (71.4 years and 72.9 years) compared to the current study, which may have also contributed to different results (Al-Delaimy et al., 2009; Doi et al., 2015).

No significant relationships between IGF-1 and cognition were seen in T2DM. This contradicts the results of Rui-Hua and colleagues, which found a positive association between IGF-1 levels and the Montreal Cognitive Assessment (MoCA) test in T2DM (Rui-Hua et al., 2019). One potential explanation for the discrepancy may be the difference in ethnic composition between study populations, as IGF-1 levels can vary across racial backgrounds (Platz et al., 1999). In the study by Rui-Hua et al., participants were recruited from Shanghai (Rui-Hua et al., 2019), whereas in the current study, participants were recruited from the United States where the majority of the participants were white. As in the abovementioned positive studies, the MoCA was used to screen for general cognitive status in that study, whereas the current study measured two specific domains of cognitive performance across different risk levels, which could account for potential differences.

Greater IGF-1 concentrations were associated with better executive function in males with prediabetes, but a negative borderline association was observed in males with T2DM. This difference has not been previously reported in the literature. One possibility could be the use of various antidiabetic agents with different mechanisms of action in the T2DM group, which could confound possible relationships between IGF-1 and cognition. Another potential explanation could be hyperinsulinemia, which can alter IGF-1 concentrations. Although results were adjusted for HOMA-IR, hyperinsulinemia might affect peripheral IGF-1 signaling in several ways. First, IGF-1 production is enhanced due to hyperinsulinemia and increased hepatic growth hormone receptor expression (Calle and Kaaks, 2004). Additionally, IGF binding protein

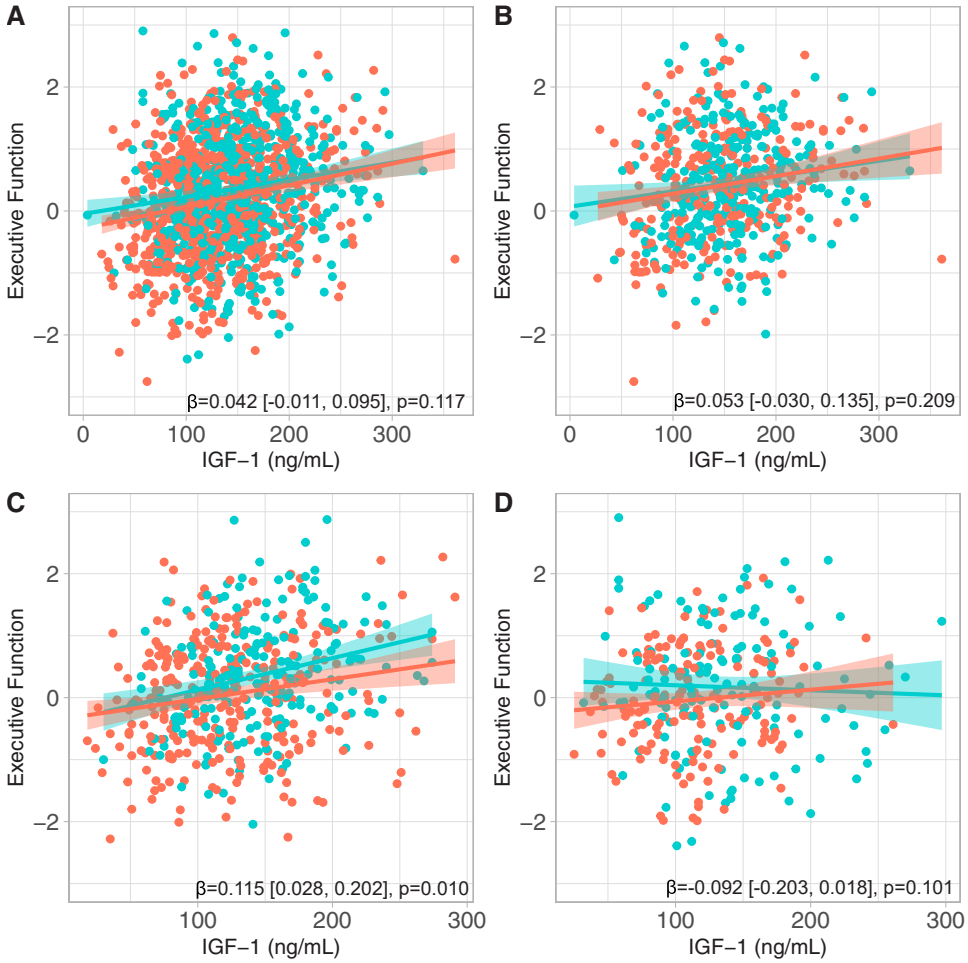

Fig. 3. Associations between IGF-1 and executive function z-score in (A) the whole sample, (B) normoglycemia, (C) prediabetes, and (D) T2DM. Males are represented in blue, and females are represented in red.

(IGFBP)−3 levels are also increased in T2DM (Clemmons, 2016). In the periphery, IGF-1 is commonly bound to IGFBP-3, which is too large to cross the blood brain barrier (Lewitt and Boyd, 2019). Therefore, it is possible that despite the increase in peripheral levels of IGF-1, it did not change brain IGF-1 concentrations to effect cognitive performance in T2DM. Insulin resistance is also associated with cognitive decline (Willmann et al., 2020); therefore, participants with high peripheral IGF-1 levels might have low cognitive performance due to other effects of insulin resistance on the brain, which may have contributed to the opposite borderline association observed in T2DM. Alternatively, IGF-1 resistance may also explain the negative borderline association in males with T2DM. In patients with Alzheimer's disease, previous studies have noted a reduced expression of IGF-1 receptor mRNA and downstream signaling of IGF-1, thereby suggesting IGF-1 resistance (Steen et al., 2005). Similarly, in individuals with T2DM, IGF-1 signaling may be impaired particularly in the brain due to IGF-1 resistance, thereby resulting in worse cognition despite high IGF-1 levels in the periphery. The present study excluded 1 participant with documented Alzheimer's disease; however, some older people with normal cognition or MCI may have incipient Alzheimer's disease and future studies might examine IGF-1 levels and effects in tandem with biomarkers for Alzheimer's disease.

A small sex difference was also observed in the prediabetes subgroup, where the positive association between IGF-1 and cognition were stronger in males than females. Sex differences have been previously reported in the literature, where a positive association between IGF-1 and cognition was found in males only (Al-Delaimy et al., 2009), yet it has not always been consistent. For instance, other studies have failed to observe any cross-sectional association between IGF-1 and cognition in males (Tumati et al., 2016), or found an association in females only (Perice et al., 2016; Wennberg et al., 2018). The reason for this is unclear, yet the study by Tumati et al., did not identify individuals with T2DM or the use of antidiabetic medication, which may have confounded the relationship, and the study by Perice and colleagues were limited in sample size, suggesting that the lack of statistical power may have resulted in a failure to detect any association in men (Perice et al., 2016). Wennberg and colleagues noted an inversed U-shaped association between IGF-1 levels and cognitive performance in women, where mid-range IGF-1 levels were associated with better cognitive performance than those with low or high IGF-1 (Wennberg et al., 2018). A theoretical explanation for possible sex differences observed in this study may be varying levels of estrogen. In the brain, estrogen receptors and IGF-1 receptors are often co-expressed, and previous studies have suggested that neuronal survival and differentiation depends on both estrogen and IGF-1 receptors (Garcia-Segura et al., 2010). Based on the age ranges in this study, it is likely that female participants of this study were at various stages of menopause. As menopause is associated with a rapid decline in both estrogen and IGF-1 levels, the association between IGF-1 and cognitive performance may have been confounded in females (Nasu et al., 1997). The MIDUS study did not measure estrogen levels, but this might be investigated in future studies.

Clinical intervention studies that aimed to increase peripheral IGF-1 levels by directly injecting IGF-1 or administering GHRH, have revealed inconsistent results (Friedlander et al., 2001; Vitiello et al., 2006). When

healthy, midlife female participants were given a subcutaneous injection of IGF-1 twice daily for one year, despite an increase in peripheral IGF-1 levels, no changes in memory performance were observed compared to the placebo group (Friedlander et al., 2001). This was in accordance with the current study, as no association between IGF-1 and memory were observed, and no cognitive associations were seen in women. Therefore, future IGF-1 therapy studies might consider executive performance, particularly in males with prediabetes. On the other hand, when healthy, midlife participants were asked to inject GHRH subcutaneously once daily for 6 months, improvements were seen in multiple cognitive domains including problem solving, psychomotor processing speed, and memory (Vitiello et al., 2006). It is possible that peripheral GHRH injection has IGF-1 independent benefits and/or that IGF-1 injection activated the negative feedback loop to suppress the release of GHRH (Nyberg and Hallberg, 2013). As that study investigated the effects of GHRH in healthy individuals, future studies might examine cognitive effects in males with prediabetes.

4.1. Limitations

Although the present study observed differential effects between groups based on diabetes status, the design of the MIDUS study relied on a self-report for medical history, medication information, and an HbA1c measure, which were collected approximately two years after cognitive assessments, to separate subgroups in this study. Therefore, the subgroups may not accurately represent the true glycemic status (i.e., normoglycemia, prediabetes, or T2DM) at the time of cognitive assessment. Future studies should re-examine the association between IGF-1 and cognition across diabetes status where all variables were collected during a single timepoint. Second, IGF-1 was not measured at the same time as cognitive assessments, and imprecision might be expected, elevating the risk of type 2 error. Future studies may consider studying the association of baseline IGF-1 with cognition over time in individuals with normoglycemia, prediabetes, and T2DM. Third, IGFBP levels were not measured in this study. As mentioned previously, IGF-1 is often bound to IGFBP in the periphery, and as a complex, IGF-1 is not biologically active, and cannot cross the blood brain barrier (Frater et al., 2018; Lewitt and Boyd, 2019). As this study measured total IGF-1 levels, this may not accurately represent the free, bioavailable levels of IGF-1 to elicit a beneficial effect on cognition. In a study by Huang and colleagues, IGF-1/IGFBP-3 molar ratio, but not total IGF-1, was lower in individuals with MCI compared to cognitively normal participants (Huang et al., 2015). Therefore, future studies should examine whether the associations differ when free IGF-1 or IGF-1/IGFBP ratios are used instead of total IGF-1 levels. Finally, a modified version of RAVLT was used to assess memory in the BTACT. Although the RAVLT has been validated and used as a measure of memory performance (Bean, 2011), the modified version has not been validated against the original form. Therefore, future studies should re-examine the association between IGF-1 and memory across different diabetes status using another validated memory test.

4.2. Conclusion

This study illustrates that the association between IGF-1 and executive performance may differ depending on diabetes status and sex, where higher IGF-1 levels were associated with better executive function in individuals with prediabetes, especially in males, yet not in participants with normoglycemia or T2DM. The results of the study suggest that diabetes status and sex are important factors to consider when examining this association and may help explain the discrepancies observed in the literature.

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CRediT authorship contribution statement

Si Won Ryoo: Conceptualization; Data curation; Methodology; Formal Analysis; Investigation; Writing – Original draft, Review and Editing; Visualization. **Natasha Z Anita**: Methodology, Writing – Review and Editing. **George Perlman**: Data curation; Writing – Review and Editing. **Lisa Y. Xiong:** Methodology; Formal analysis; Writing – Review and Editing. **Che-Yuan Wu**: Methodology; Writing – Review and Editing. **Madeline Wood**: Writing – Review and Editing; **Jennifer S. Rabin:** Writing – Review and Editing. **Jane Mitchell**: Conceptualization; Writing – Review and Editing. **Walter Swardfager**: Conceptualization; Funding acquisition; Methodology; Supervision; Writing – Review and Editing.

Declaration of Competing Interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106946.

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