

Background

- Type 2 Diabetes Mellitus (T2DM) is associated with increased risk for Alzheimer's disease, which is more pronounced in females than males^{1,2}
- Glycosylated hemoglobin (HbA1c) is used to monitor risk and diagnose T2DM; prediabetes (HbA1c: 6.0-6.4%) is associated with higher risk for T2DM and poorer executive functioning^{3,4}
- T2DM is associated with accelerated progression to dementia in persons with mild cognitive impairment (MCI)⁵
- Sex differences in T2DM pathophysiology, metabolic dysfunction, and downstream cognitive outcomes may also affect cognitive decline in MCI⁶⁻⁸
- Few studies have explored the sex-specific associations between hyperglycemia and indices of brain health in non-diabetic individuals with MCI

Objectives

- To examine the association between HbA1c and brain structure/cognition in individuals with MCI
- To examine the sex-stratified, moderating role of diabetic status on the relationship between brain structure and cognition in MCI

Hypotheses

- Higher HbA1c will be associated with poorer cognition and smaller brain volume
- Greater brain volume will be associated with better cognition in normoglycemic individuals, but this relationship will be attenuated or disrupted in prediabetic individuals

Method

Dataset

- Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) Study⁹
- Inclusion criterion: Diagnosis of amnesic MCI

Measures

- Screening visit: MCI diagnosis, demographic information
- Clinical visit: HbA1c
- Neuropsychology visit: Rey Auditory Verbal Learning Task (RAVLT), Digit Symbol Substitution Test (DSST), Digit Span (DS), Trail Making Test-B (TMT-B)
 - Executive Function (EF) composite: DS raw score, DSST raw score, and TMT-B completion time
 - Memory composite: DSST free recall, RAVLT immediate and extended delay recall scores
 - Supplementary process scores:
 - Interference: RAVLT intrusions
 - Perseveration: RAVLT repetitions
- MRI visit: Gray Matter Volume (GMV), frontal GMV, White Matter Volume (WMV), left and right Hippocampal Volume (HCV)

Analyses

- Multiple linear regression (R Studio 4.3.1¹⁰)
 - Brain volume ~ HbA1c + age + education + sex
 - Cognition ~ HbA1c + age + education + sex
- Sex-stratified moderation:
 - Cognition ~ Brain volume * diabetic status + age + education

Results

Descriptives (N=370)

Variable	Overall Sample (N = 370)			Female Sample (N = 164)			Male Sample (N = 206)		
M±SD or n(%)	Diabetic	Normal	Prediabetic	Diabetic	Normal	Prediabetic	Diabetic	Normal	Prediabetic
N	41 (11.08%)	278 (75.14%)	51 (13.7%)	15 (9.15%)	129 (78.66%)	20 (12.20%)	26 (12.62%)	149 (72.33%)	31 (15.05%)
Age (years)	72.89 ± 5.64	73.27 ± 6.87	73.85 ± 7.66	70.31 ± 4.12	72.91 ± 6.8	72.22 ± 7.07	74.46 ± 5.92	73.6 ± 6.95	74.88 ± 7.96
Education (years)	14.73 ± 3.14	15.09 ± 2.71	14.59 ± 3.49	15.2 ± 2.04	14.72 ± 2.83	13.55 ± 3.72	14.46 ± 3.64	15.4 ± 2.58	15.26 ± 3.21
HbA1c (%)	7.02 ± 0.41	5.47 ± 0.27	6.16 ± 0.16	7.05 ± 0.43	5.49 ± 0.28	6.18 ± 0.17	7 ± 0.41	5.47 ± 0.26	6.14 ± 0.15

Association between HbA1c and Cognition in Persons with MCI

Controlling for age, sex, and education, HbA1c was positively associated with memory composite scores ($\beta = 0.12$, $p = .02$, $r^2 = 0.01$; Figure 1). Associations were not statistically significant for EF composite or volumetric variables (p -range: .21 - .96).

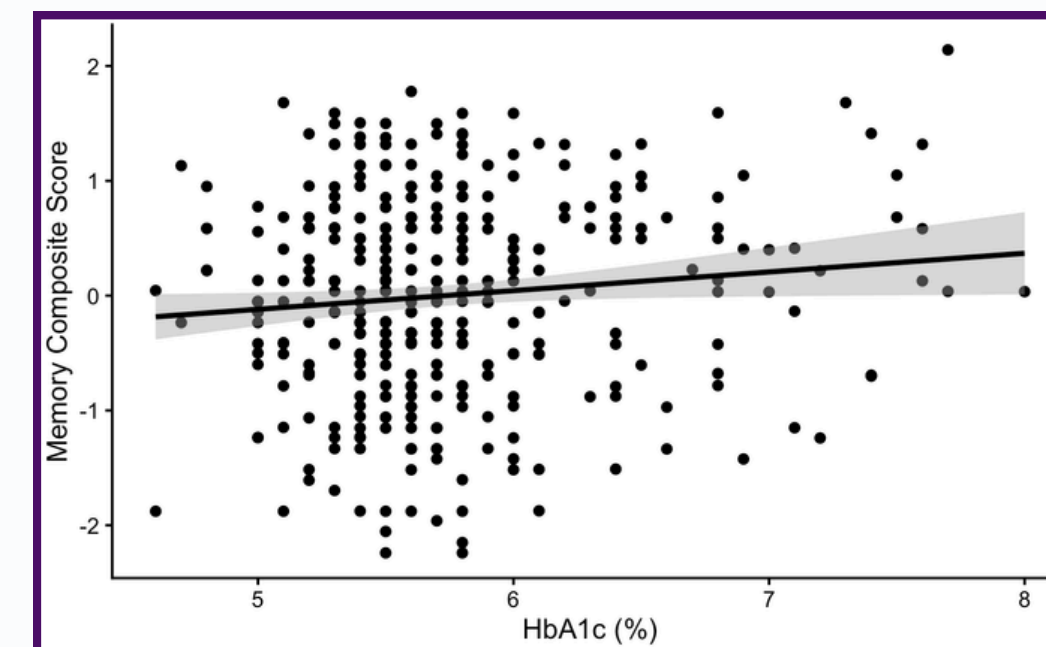


Fig 1. HbA1c and memory composite score adjusted for age, education, and sex

Sex-Stratified Moderating Role of Diabetic Status in the Brain-Cognition Relationship

In Females: Greater WMV was associated with better EF in normoglycemic females ($R^2 = .13$, $F(5, 137) = 4.27$, $p = .001$; $\beta = 0.24$, $p = .011$, $r^2 = 0.03$), and this relationship was reversed in prediabetic females ($\beta = -0.47$, $p = .012$, $r^2 = 0.05$; Figure 2a). Greater frontal GMV was associated with better memory in normoglycemic females ($R^2 = .10$, $F(5, 137) = 3.05$, $p = .012$; $\beta = 0.30$, $p < .001$, $r^2 = 0.07$), and this relationship was also reversed in prediabetic females ($\beta = -0.48$, $p = .044$, $r^2 = 0.03$; Figure 2b).

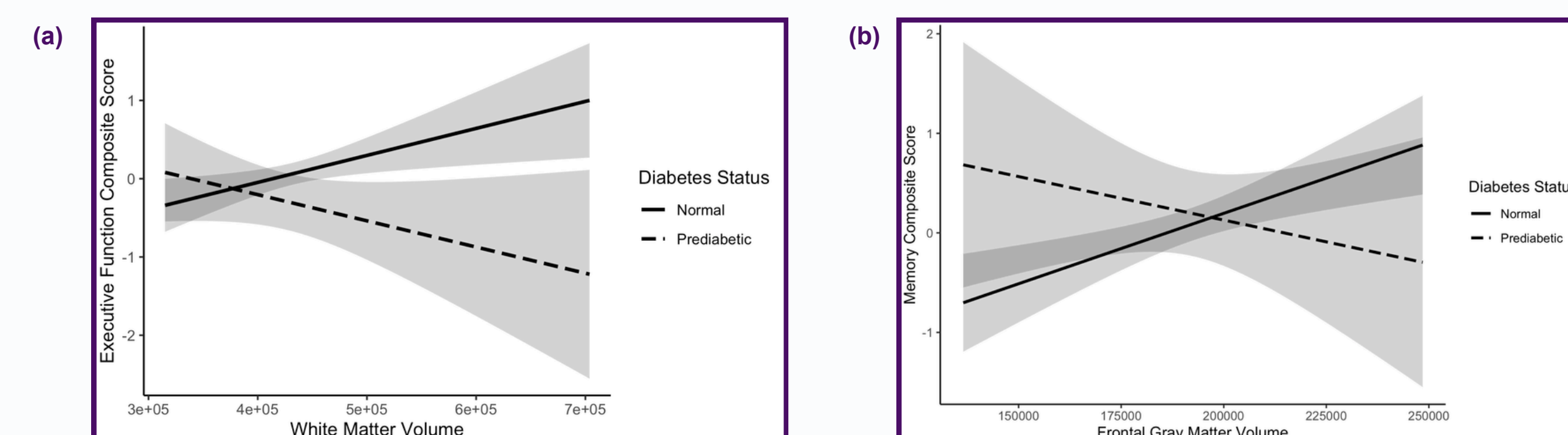


Fig 2. Moderating effect of diabetic status on brain structure and cognition in females

In Males: Greater GMV was associated with more RAVLT intrusions in prediabetic ($R^2 = .10$, $F(5, 153) = 3.41$, $p = .006$; $\beta = 0.68$, $p = .002$, $r^2 = 0.07$), but not normoglycemic males ($\beta = -0.06$, $p = .478$, $r^2 < 0.01$; Figure 3a). Greater left HCV was associated with more RAVLT intrusions in prediabetic males ($R^2 = .09$, $F(5, 153) = 3.07$, $p = .011$; $\beta = 0.55$, $p = .005$, $r^2 = 0.05$; Figure 3b), but this was reversed in normoglycemic males ($\beta = -0.18$, $p = .045$, $r^2 < 0.01$). Greater right HCV was trending toward an association with fewer RAVLT intrusions in normoglycemic ($R^2 = .09$, $F(5, 153) = 2.97$, $p = .014$; $\beta = -0.17$, $p = .057$, $r^2 < 0.01$), but not prediabetic males ($\beta = 0.58$, $p = .007$, $r^2 = 0.05$; Figure 3c).

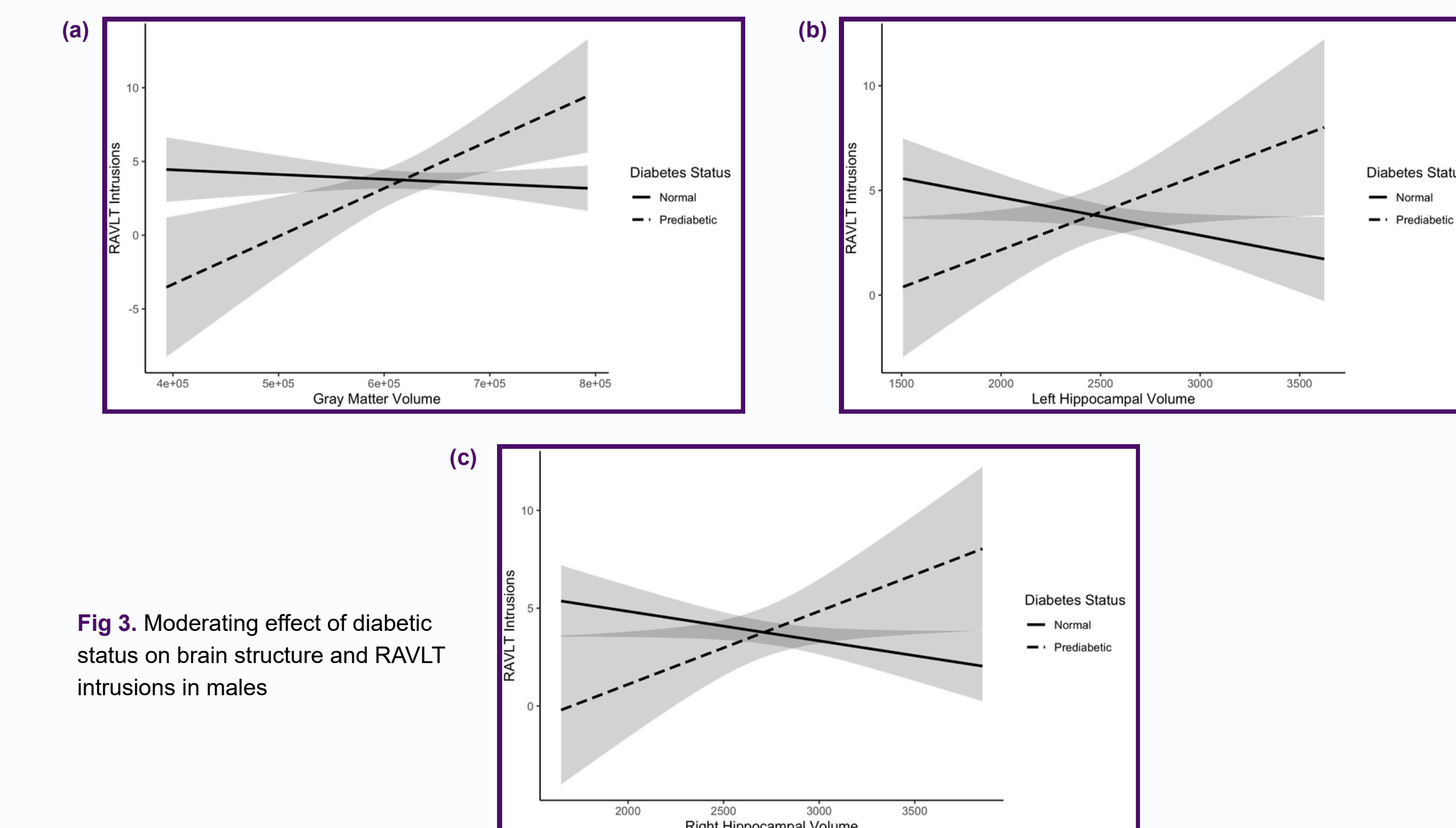


Fig 3. Moderating effect of diabetic status on brain structure and RAVLT intrusions in males

Discussion

- HbA1c was positively associated with memory performance across both sexes, in contrast to previous evidence
 - Potentially representative of the influence of systolic blood pressure, adiposity, and resting state functional connectivity factors (not assessed in this study)¹¹⁻¹³
- In prediabetic females with MCI, higher WMV and frontal GMV did not correspond to better EF and memory performance, respectively
- In prediabetic males with MCI, higher GMV, and left and right HCV did not correspond to lower memory interference
- Overall, in prediabetic females and males with MCI:
 - Greater WMV may be indicative of microstructural abnormalities, contributing to poorer EF and memory^{14,15}
 - Greater GMV may be indicative of neuroinflammation and structural abnormalities, contributing to poorer memory¹⁶

Strengths

- Leveraging a multi-modal dataset encompassing cognitive, neuroimaging, and glycemic measures, this study provides a comprehensive characterization of the relationship between hyperglycemia and brain health in Canadians with MCI
- By assessing the moderating role of diabetic status on brain-cognition relationships, findings advance understanding of early, sex-differentiated metabolic risk pathways for dementia progression and highlight glycemic control as a clinically meaningful and modifiable intervention target

Limitations

- Cohort is highly homogeneous in terms of race (88% white)
- Sex-specific risk factors (e.g., *Apolipoprotein-E4* status, menopause type, depression) not examined
- Gender as a variable was not available at the first timepoint; gendered experiences may influence upstream determinants of biological factors such as diet, income, and education

Conclusion

Findings suggest that sub-diabetic elevations in HbA1c may differentially disrupt brain-cognition relationships in females and males with MCI, underscoring the importance of early glycemic monitoring and sex-stratified approaches in efforts to mitigate dementia risk.

References

Scan QR code for references and the digital poster.



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