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Glycemia and cognitive function in metabolic syndrome and coronary heart disease

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Abstract

Objective—Higher hemoglobin A_{1c} (HbA_{1c}) is associated with lower cognitive function in type 2 diabetes. To determine if associations persist at lower levels of dysglycemia in patients who have established cardiovascular disease, cognitive performance was assessed in the Targeting Inflammation Using Salsalate in Cardiovascular Disease (TINSAL-CVD) trial.

Research Design and Methods—The age-adjusted relationships between HbA_{1c} and cognitive performance measured by the Mini-mental State Examination (MMSE), Digit Symbol Substitution Test (DSST), Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test (TMT), and Categorical Verbal Fluency (CVF) were assessed in 226 men with metabolic syndrome and established stable coronary artery disease.

Results—61.5% of participants had normoglycemia, 20.8% impaired fasting glucose, and 17.7% type 2 diabetes. HbA_{1c} was associated with cognitive function tests of DSST, RAVLT, TMT and CVF (all $P<0.02$), but not MMSE. In an age-adjusted model, a 1% (11 mmol/mol) higher HbA_{1c} value was associated with a 5.9 lower DSST score (95%CI: −9.58 to −2.21; $P<0.0001$); a 2.44 lower RAVLT score (95%CI: −4.00 to −0.87; $P<0.0001$); a 15.6 higher TMT score (95%CI: 5.73 to 25.6; $P<0.0001$); and a 3.71 lower CVF score (95%CI: −6.41 to −1.01; $P<0.02$). In multivariate model adjusting for age, education and cardiovascular covariates, HbA_{1c} remains associated with

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*Please note work by co-authors Corinne Barbato, Winnie Wong, Sherine Thomas, and Camille Paul were performed while at Joslin, however, they have moved onto graduate training programs.

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cognitive function tests of RAVLT (R^2=0.27, P<0.0001), TMT (R^2=0.18, P<0.0001), and CVF (R^2=0.20, P<0.0001) although association with DSST was reduced.

Conclusion—Higher HbA_{1c} is associated with lower cognitive function performance scores across multiple domain tests in men with metabolic syndrome and coronary artery disease. Future studies may demonstrate whether glucose lowering within the normative range improves cognitive health.

Keywords

Cognitive Function; Hemoglobin A1c; glycemia; cardiovascular disease

Introduction

Mild cognitive impairment is common and may precede frank dementia. About 19% of persons above age 65 years and 29% above 85 years have mild cognitive impairment [1], representing a substantial population health issue among older persons. Persons with coronary artery disease and those with type 2 diabetes are both at higher risk of cognitive impairment [2–4]. More patients with cardiovascular disease have dysglycemia, diabetes or prediabetes, than normoglycemia [5].

Cognitive function is associated with glycemia in patients with type 1 or type 2 diabetes [6–8]. Cognitive function declines with acute hyperglycemia [9] or hypoglycemia [10, 11]. Working memory may improve in patients with type 2 diabetes with improving metabolic control [12]. The Memory in Diabetes (MIND) substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial established an association between higher age-adjusted HbA_{1c} and lower cognitive function in patients with type 2 diabetes [13] at high cardiovascular risk and with HBA_{1c} above 7.5% (58.5 mmol/mol) at study entry. As dysglycemia is highly prevalent in patients with cardiovascular disease, we sought to determine if the association between glucose and cognitive dysfunction was also present at lower levels of dysglycemia than in the ACCORD study population, as this could have substantial impact on general health of patients with coronary heart disease, including medication adherence and quality of life. Thus, we evaluated the relationship between HbA_{1c}, and cognition in a complementary cohort to the ACCORD-mind with stable coronary artery disease and HbA_{1c} below 7.5% (58.5 mmol/mol), spanning the range from normal to pre-diabetes and well-controlled diabetes.

Research Design and Methods

Study was approved by the Joslin Diabetes Center Institutional Review Board. Subjects provided informed written consent. This study was conducted as an ancillary investigation in the trial Targeting INflammation Using SALsalate in CardioVascular Disease (TINSAL-CVD, ClinicalTrials.gov Identifier: NCT00624923). The aim of the parent study is to determine efficacy of targeting inflammation using salsalate to reduce progression of non-calcified coronary artery plaque volume assessed by multi-detector computed tomography angiography over 30 months. A sub-aim of the study is to assess the effects of targeting inflammation on cognitive function. Only baseline data was used in this analysis.

Participants include community-dwelling adult males with metabolic syndrome, fluent in the English language, under the age of 75 years, with body mass index between 27–40 kg/m^2, metabolic syndrome, and established coronary artery disease including previous myocardial infarction or coronary artery bypass, stable angina, abnormal cardiac exercise or pharmacologic stress test, or plaque by prior imaging in at least one coronary artery. All participants were using statin class agents, and had estimated Cockcroft-Gault creatinine clearance above 60 ml/min [14]. Persons with prior stroke, malignancy, tinnitus, gastric bypass surgery, gastrointestinal bleeding, alcohol use exceeding 14 units/week, using chronic thiazolidinediones, insulin, glucagon-like peptide-1 agonists, corticosteroids, nonsteroidal anti-inflammatory drugs, warfarin, or uricosuric agents, were excluded from the parent study. Women represent under 6% of the parent study population, so were excluded from sub-study analysis. Participants with poor glycemic control (HbA_{1c} above 7.5% (58.5 mmol/mol)) were excluded *a priori* to maintain focus of investigation on persons spanning normal to moderate dysglycemia. The mean of three blood pressure measurments was used. Blood was collected after overnight fast for HbA_{1c}, glucose, lipids, and creatinine (Quest Laboratories, Cambridge, MA). Table 1 summarizes cognitive measurement tools performed by a trained study coordinator after participants had a light standardized meal.

Statistical Methods

Linear regression was used to assess the relationship of each measure of cognitive status with HbA_{1c}, and control for potential confounding factors, including age, education, smoking status, body mass index (BMI0, blood pressure, non-high density lipoprotein (HDL) cholesterol, short form-36 (SF-36) Mental Score, and history of depression. The age-adjusted relationship between HbA_{1c} and cognitive measure was the primary endpoint (Model 1). The age-adjusted analysis was repeated in a sub-set excluding those with type 2 diabetes (Model 2). Model 3 included age and education adjustment. Model 4 included all covariates listed above. β-coefficient estimates are provided with 95% confidence limits and as standardized estimates. *P*-values below 0.05 were considered significant. All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Demographic and clinical characteristics of study participants are described in Table 2. 61.5% had normoglycemia, 20.8% impaired fasting glucose, and 17.7% type 2 diabetes. 97.3% of participants had normal cognition based on Mini Mental State Examination scores of 25 or above, and no participant had scores consistent with moderate or severe dementia. HbA_{1c} was not associated with the Mini Mental State Examination score in any model. However, in bivariate analysis, HbA_{1c} was associated with scores on Digit Symbol, RAVLT Word Learning, Trailmaking B and Categorical Verbal Fluency (all $P<0.02$) (Figure 1). In models including HbA_{1c} and age (the primary endpoint) (Table 3, **Model 1**), the variance explained by the models for these four cognitive tests improved compared with HbA_{1c} alone, and higher HbA_{1c} remains associated with lower cognitive function. Specifically in the age-adjusted model for the full population a 1% higher HbA_{1c} value was associated with a 5.9 lower Digit Symbol score (95% CI: −9.58 to −2.21; $P<0.0001$); 2.44 lower RAVLT Word Learning score (95%CI: −4.00 to −0.87; $P<0.0001$); 15.6 higher Trailmaking B score

(95%CI: 5.73 to 25.6 $P<0.0001$); and 3.71 lower Categorical Verbal Fluency test score (95%CI: −6.41 to −1.01; $P<0.02$). Considering only the sub-cohort without diabetes, in age-adjusted models higher HbA_{1c} remained associated with lower cognitive function in Digital Symbol, Rey Word Learning, and Trailmaking B scores, although significance was not retained for Categorical Verbal Fluency (Table 3, **Model 2**).

Likewise in models adjusting for age and education (Table 3, **Model 3**), the model predictive values are improved for these four cognitive tests compared with HbA_{1c} alone, and HbA_{1c} as a covariate remains associated with cognitive function, with the exception of Categorical Verbal Fluency where significance for HbA_{1c} is reduced.

In a model adjusted for age, education, age and cardiovascular and depression covariates (Table 4, **Model 4**), HbA_{1c} remains associated with cognitive function tests of Rey Word Learning, Trail Making, and Categorical Verbal Fluency (all $P<0.0001$), although association with Digital Symbol score was reduced. Furthermore, in standardized parameter estimates HbA_{1c} was the top ranking covariate, after age and education, associated with cognitive function for each test.

In contrast, while there was an association in unadjusted analysis between HbA_{1c} and cognitive functions captured by the Rey Auditory Verbal Learning Test immediate recall (sum of four trials, Figure 1C), Short Delay for List A ($R^2=0.0284$, $P=0.011$), and Delay Recall for List A ($R^2=0.0216$, $P=0.027$), the association between HbA1c and the delayed components did not remain significant when considering age, education, and/or cardiovascular and depression covariates.

Fasting glucose on the morning of testing was correlated with Digit Symbol Substitution Test ($R^2=0.032$, $P=0.006$) and Trail Making A score ($R^2=0.025$, $P=0.02$), but not the other test components or the Mini Mental State Exam. In age-adjusted models, fasting glucose on the morning of testing remained associated with Digit Symbol Substitution Test score (95%CI: −0.21 to −0.01; $P=0.028$); but the association was lost when other covariates were added.

Discussion

We demonstrate an association between cognitive function and glycemia assessed by HbA_{1c} in men with stable coronary artery disease spanning a range of normal to moderately abnormal glucose metabolism. Age and education are important determinants of cognitive function [15] and the association between cognitive function and glycemia remains significant in age-, and age- and education-adjusted models. HbA_{1c} remains associated with cognitive function when cardiovascular risk factors, depression, and SF-36 mental status are also included in the model. These findings are important given the increased prevalence of pre-diabetes and diabetes, cardiovascular disease, and cognitive impairment ranging from mild to frank dementia in the elderly, and the negative role cognitive impairment in patients with mild dysglycemia could play on individual capacity to adhere with complex cardiovascular treatment recommendations, together providing substantial importance to identify therapeutic targets for treatment and prevention of cognitive decline.

Vascular dementia may contribute substantially to cognitive decline, both in those with coronary artery disease and type 2 diabetes [2, 3]. Additionally, about 5% of adults aged 65–74 and 50% 85 years and older in the United States have Alzheimer's disease [16]. About 22% of the same population (aged 65–74) has been diagnosed with diabetes, and the prevalence of abnormal glucose tolerance is substantially higher when including those with undiagnosed diabetes and pre-diabetes [17]. The two disorders frequently co-occur and type 2 diabetes has been associated with cognitive impairment [6–8, 13], accelerated cognitive decline [18–20], and higher risk of Alzheimer's disease [21–23]. Furthermore, cognitive impairment less severe than dementia may impair quality of life and independence. Thus, it is of public health importance to better understand the relationship between glycemia and cognitive function, especially in persons with coronary artery disease, in whom multiple mechanisms may contribute to impaired function.

Acute hypoglycemia has been associated with reduced mental function [10]. Likewise, increased glycemia has been associated with poorer cognitive function. In longitudinal analysis, self-reported diabetes was associated with incident all cause, amnestic, and non-amnestic mild cognitive impairment [24]. Longer duration and severity of diabetes are important determinants of mild cognitive impairment [8]. The ACCORD-Mind demonstrated an age-adjusted association between HbA_{1c} and cognitive function in patients with mean diabetes duration of 10 years and HbA_{1c} above 7.5% (58.5 mmol/mol) at study entry, with mean of 8.3% (67.2 mmol/mol) [13]. Our studies extend the association between HbA_{1c} and cognitive dysfunction into more modest degrees of dysglycemia (below 7.5%, 58.5 mmol/mol) in men with metabolic syndrome and stable coronary artery disease, to levels that would be considered non-diabetic to medically well controlled.

We found associations between age and education with cognitive function, consistent with studies in the general population and in those with diabetes [15, 25, 26]. Our studies are also consistent with those showing association between HbA_{1c} and cognitive function in type 2 diabetes [8, 13, 15, 27], and in pre-diabetes and well glycemic controlled diabetes [28], but extend these findings into a population with established coronary heart disease. Our study demonstrates the similar strength of association after adjustment for age and education between HbA_{1c} multiple cognitive domains as captured by scores for Digital Symbol, Rey Word Learning Test, and Trail Making B, but less strong association with Categorical Verbal Fluency. Additionally, between 72–96% of the strength of association between HbA_{1c} and cognitive function in unadjusted analysis is retained when adding age to the model, and 48–64% retained when both age and education are considered. Moreover, in the sub-cohort without diabetes, HbA_{1c} remained associated with Digital Symbol Substitution Test, Rey Auditory Verbal Learning Test, and Trail Making B, although did not remain associated with Categorical Verbal Fluency. This may be due to reduced power in this smaller group, suggested by the relatively similar beta and standardized estimates compared with the full cohort. It is also possible cognitive performance in this test of verbal production, semantic memory and language [29] is not associated with HbA_{1c}, as suggested by reduced association in the model including age, education and cardiometabolic variables and the analysis limited solely to the non-diabetic HbA_{1c} glycemic range.

Multiple cognitive tests were administered, and higher HbA_{1c} was related to poorer performance across multiple functional domains including aspects of executive function, speed of processing, and language. While digit substitution and the auditory-verbal learning component Rey Auditory Verbal Learning Test were associated with glycemia, we found only weak association between HbA_{1c} and the memory component in the Rey Auditory Verbal Learning Test (short delay or delay recall) which did not remain significant when adjusted for covariates, and no association was found between HbA_{1c} and the memory component of the Mini-Mental State Examination. These findings are consistent with studies showing strongest associations between poor glucose tolerance and lower verbal fluency, although others have not found this relationship in persons with impaired glucose tolerance [30].

Importantly, our study cohort did not have dementia, so associations with mild to moderate dementia would not be detectable. The ranges of cognitive tests scores in our cohort are similar to those considered to be a cognitively normal, non-diabetic US sample [31]. The Mini-Mental State Examination was not associated with glycemia in our cohort similar to studies in persons without dementia [30]. It is possible associations would be found in cohorts including greater proportion with compromised cognition.

Association between HbA_{1c} and cognitive function does not establish causality. It is plausible patients with better cognition also adhere to or make better lifestyle choices and thus have lower HbA_{1c}. It is also possible HbA_{1c} is a biomarker for severity of vascular disease and/or other factor(s) influencing cognition. We found stronger association between HbA_{1c}, than fasting glucose on the morning of testing. Our study was limited by the measure of fasting blood sugar and administration of cognitive function testing after a meal, such that immediate measure of immediate glucose concentration during testing is not available. There is no evidence dietary composition of a preceding meal influences cognitive function [32]. Our findings may not be applicable to women. Statins may be associated with cognitive dysfunction. All participants were using statins, but type and dose varied. Finally our study was cross-sectional, and we cannot infer on decline.

In our cohort with established coronary heart disease, we found HbA_{1c} associated with cognitive function tests of Digit Symbol Substitution Test, Rey Auditory Verbal Learning Test, Trail Making and Categorical Verbal Fluency but not Mini-Mental State Examination. Associated tests mainly measure speed of processing, memory and executive functions [33]. These findings are consistent with reduced neuronal functional connectivity in patients with type 2 diabetes compared with non-diabetic controls in the frontal-parietal and temporal areas of the brain [34] anatomic areas mainly relate to cognitive functions of speed of processing, memory and executive functions [33], and in white matter and the default-mode network, an area that includes the posterior cingulate cortex and temporoparietal posterior association cortical regions of the brain [34–36]. Higher HbA_{1c} also correlates with reduced hippocampal volume and microstructure [28]. Longer disease duration and elevated fasting blood glucose levels are associated with lower grey matter volume in T2D patients [20]. Our study did not measure brain structure, so whether associations between HbA_{1c} and cognitive function are mediated by structural changes needs further confirmation. However, if hyperglycemia leads to differences in brain structure, it is important to consider it may not

be possible to recover function following chronic exposure that has caused structural change to the adult brain.

Multiple cellular and molecular mechanisms may underlie structural changes in brain and/or the relationship between HbA_{1c} and cognitive impairment, including direct or indirect effects of dysglycemia on vascular disease, glycation products which may alter signal transduction pathways or metabolic intermediates [37, 38], neuronal mitochondrial function or oxidative stress, endoplasmic reticulum stress, or inflammation, insulin resistance, or the effect of insulin degrading enzyme activity on clearance of brain amyloid β [39–41], or other factors associated with HbA_{1c}.

Accelerated cognitive decline is dependent on both duration of diabetes and glycemic control [20]. Effects of glycemic improvement on cognitive function remain incompletely understood. One study demonstrated improvement over 24 weeks treatment with sulfonylurea or metformin [12]. In contrast, neither the ACCORD-mind or the Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION) study demonstrated improved cognitive function in the intensive compared with standard treatment groups [27, 42]. Hypoglycemia, which was more common in the ACCORD-mind intensive treatment group compared with standard-of-care, might have confounded potential benefits of glucose-lowering. Conceivably, slower rates of cognitive decline might occur using anti-hyperglycemic approaches not associated with hypoglycemia. In the ADDITION trial, both intensive and routine treatment groups had improvement in HbA1c (7.3% (56.3 mmol/mol) to 6.2% (44.3 mmol/mol) intensive, and 7.3% (56.3 mmol/mol) to 6.5% (47.5 mmol/mol) control, at baseline and final visit respectively). The glycemic difference between treatment groups may be insufficient to demonstrate effects of glycemic lowering on cognitive decline. There were multi-factorial metabolic interventions in the ADDITION trial, including antihypertensive and lipid lowering medications. Statin addition or other factors could confound cognitive improvement. Once cognitive function is lost over extended time it may not be regained in older adults, so understanding factors associated with and efforts to prevent early loss remain highly important.

In conclusion, higher HbA_{1c} concentrations, even across the range from normal to pre-diabetes and well controlled diabetes, are associated with lower cognitive function performance scores across multiple domains in men with metabolic syndrome and cardiovascular disease. Lower cognitive function may impact quality of life and adherence to complex treatment regimins. Future studies may demonstrate whether glucose lowering within the normative range improves cognitive health or prevents progressive decline.

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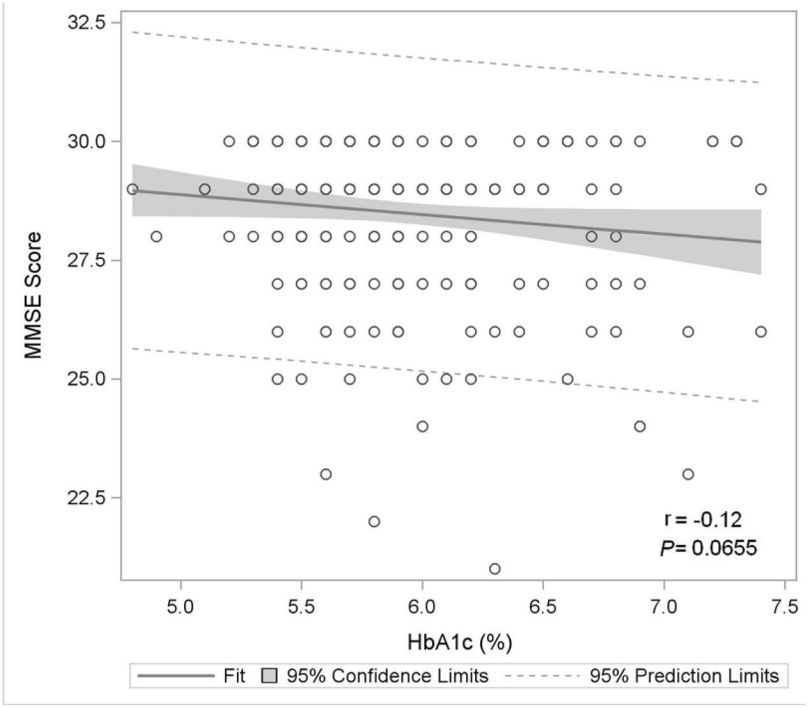
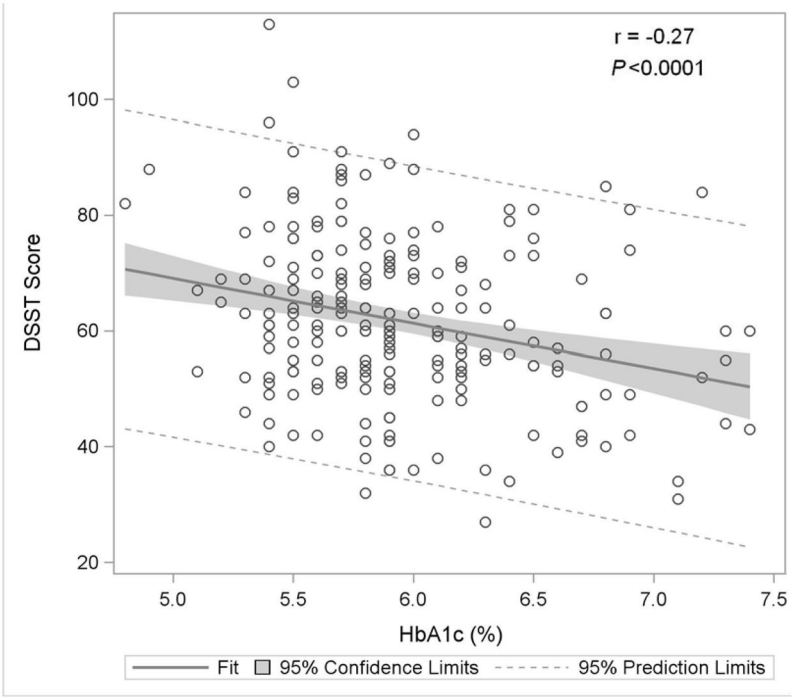
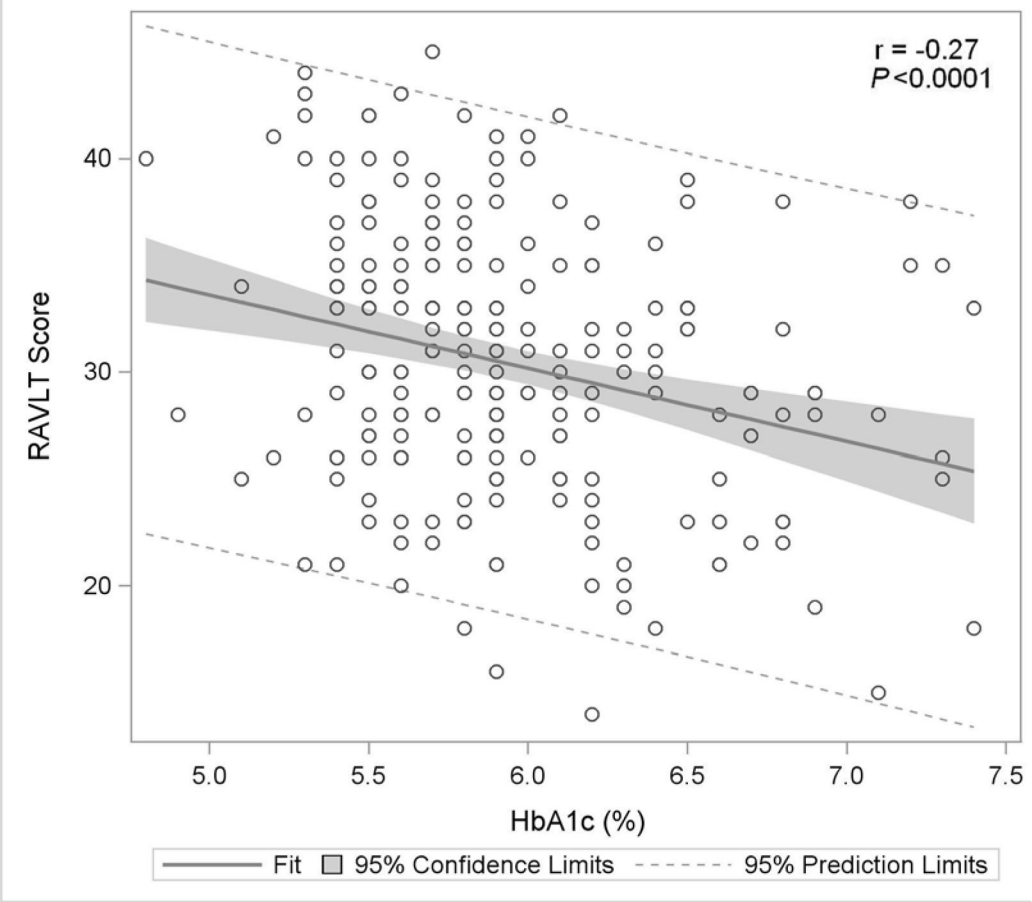
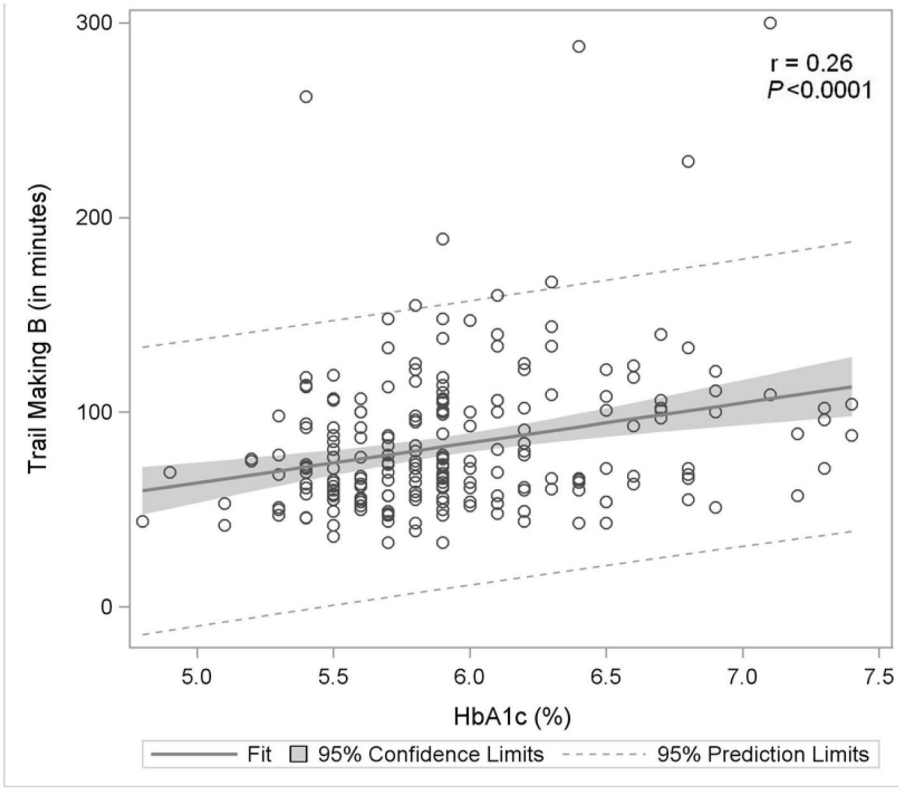
Clinical Significance

- Higher HbA_{1c}, a measure of average glucose concentrations over 2 months, is associated with lower cognitive function in type 2 diabetes.
- The association between HBA_{1c} and cognitive function extends into the glycemic range that would be considered non-diabetic to well controlled disease, in men with metabolic syndrome and stable coronary artery disease.
- Demonstrating that this relationship occurs is important to understand the pathophysiology and develop novel therapeutic approaches.









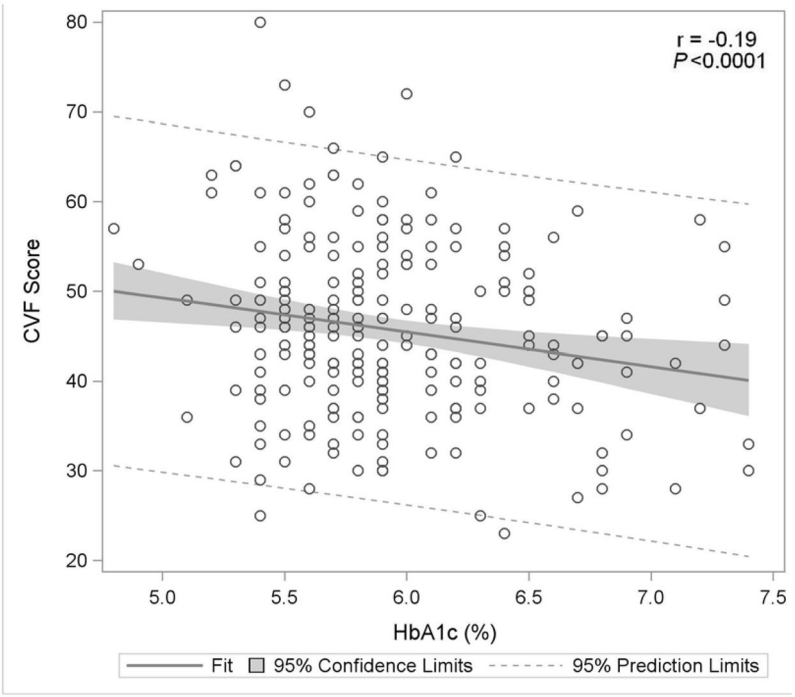


Figure 1. Association of Glycemia with Measures of Cognitive Function

Figure 1A: Mini-Mental State Exam

Figure 1B: Digit Symbol Substitution Test

Figure 1C: Rey Auditory Verbal Learning Test

Figure 1D: Trail Making Test B

Figure 1E: Categorical Verbal Fluency

Figure 1 displays in the full study cohort population scatterplots showing correlation, fitted regression, and 95% confidence intervals relating Hemoglobin A1c and cognitive function tests [A] Displays the fit plot for regression of Mini-mental state examination (MMSE) and Hemoglobin A_{1c} (HbA_{1c}). There is no association between HbA_{1c} and Mini-Mental State Examination score (P=0.07). [B] Displays the fit plot regression for Digit Symbol Substitution Test (DSST) and HbA_{1c}. The average DSST score of a patient changes by $\hat{\beta}$ = −7.79 units for each unit change in HbA_{1c} (r=−0.27, P<0.0001), [C] Displays the fit plot for regression of Rey Auditory Verbal Learning Test (RAVLT) and HbA_{1c}. The average RAVLT score of a patient changes by $\hat{\beta}$= −3.44 units for each unit change in HbA_{1c} (r= −0.27, P <0.0001). [D] Displays the fit plot for regression of Trail Making B and HbA_{1c}, The average Trail Making B score of a patient changes by $\hat{\beta}$=20.6 units for each unit change in HbA_{1c} (r=0.27, P<0.0001) and [E] Displays the fit plot for regression of Categorical Verbal Fluency (CVF) and HbA_{1c}. The average CVF score of a patient changes by $\hat{\beta}$= −3.82 units for each unit change in HbA_{1c} (r=−0.19, P=0.0042). To convert HbA_{1c}: HbA_{1c}(%) = [0.09148 * HbA_{1c} (mmol/mol)] + 2.152.

Table 1

Cognitive Function Tests Administered

A description of the cognitive function tools, functional domains evaluated in the tests, and scoring process is provided.[29]

Cognitive Function Test	Acronym	Test Assessment	Scoring
Mini-Mental State Exam	MMSE	Brief screen for dementia-orientation to time and place, memory, attention, calculation, language and visual-spatial skills	Number of correctly completed questions of problems answered correctly out of possible total of 30
Digit Symbol Substitution Test	DSST	Psychomotor performance including sustained attention, response speed and visuo-motor coordination	Number of symbols correctly matched with their corresponding digit in a minute
Rey Auditory Verbal Learning Test	RAVLT	Immediate verbal memory and learning	Average number of words recalled (0–15) over the immediate (reported as sum of four trials), short, and delayed recall trials
Trail Making Test	TMT	Complex visual scanning, attention and ability to shift between the tasks	Subject must first connect consecutively numbered circles (Part A) and then connect the same number of consecutively numbered and lettered circles alternating between the two sequences (Part B)
Categorical Verbal Fluency	CVF	Language, memory and fluency of speech	Number of items from each category (animals and supermarket items) named in 60 seconds
Short-Form (36) Health Survey	SF-36	Patient Reported Outcomes of health reflecting aspects of physical function, mental health, and quality of life	Self-administered 36 questions survey

(ref: Lezak MD: *Neuropsychological Assessment.* New York, NY, Oxford University Press, 2004)

Table 2

Baseline Characteristics of TINSAL-CVD male participants with cognitive function tests

Continuous data are presented as the mean and standard deviation or median and interquartile range and categorical data as counts and percentages.

Variable	Result	Conventional Unit
N	226	
Male sex (%)	226 (100.0)	
Race/Ethnicity		
- Caucasian	212 (93.8)	
- African American	4 (1.8)	
- Asian	5 (2.2)	
- Multi-Racial	5 (2.2)	
Age (years)	61 ± 6.9	
Weight (kg)	96.9 ± 12.0	
BMI (kg/m^2)	31.4 ± 3.0	
Waist Circumference (cm)	107.7 ± 8.6	
Blood Pressure		
- Systolic (mmHg)	128 ± 12.7	
- Diastolic (mmHg)	75 ± 8.0	
- Mean Arterial Pressure (mmHg)[a]	93 ± 8.5	
- Heart Rate (bpm)	61 ± 9.6	
Glycemia[b]		
- Normal Glucose Tolerance	139 (61.5)	
- Impaired Fasting Glucose	47 (20.8)	
- Type 2 Diabetes	40 (17.7)	
Cardiac Risk Factor History		
- Hypertension	153 (67.7)	
- High LDL Cholesterol	200 (88.5)	
- Low HDL Cholesterol	173 (76.6)	
- High Triglycerides	140 (62.0)	
- Smoking Status[c]		
○ Current Smoker	37 (16.4)	

Variable	Result	Conventional Unit
○ Former Smoker	64 (28.3)	
○ Non Smoker	125 (55.3)	
Past Medical/Surgical History		
- Coronary Heart Disease		
○ Previous Myocardial Infarction	141 (62.4)	
○ Stable Angina	89 (39.4)	
○ Angioplasty/Stent	152 (67.3)	
○ Previous Coronary Artery Bypass Surgery	54 (23.9)	
○ Abnormal Exercise Tolerance Test	88 (38.9)	
○ Significant Non-Calcified Plaque	5 (2.21)	
- Vascular Disease		
○ Stroke	4 (1.8)	
○ Transient Ischemic Attack	3 (1.3)	
○ Carotid Vascular Disease	6 (2.7)	
○ Carotid Endartectomy	3 (1.3)	
○ Peripheral Vascular Disease	9 (4.0)	
○ Peripheral Artery Bypass Surgery	3 (1.3)	
○ Peripheral Artery Angioplasty	3 (1.3)	
- Psychological[d]		
○ Depression	37 (16.4)	
○ Counseling for Psychological Problems	25 (11.1)	
○ Medicines for Psychological Problems	22 (9.8)	
○ Anxiety	9 (4.0)	
Years of School Completed		
- 11–14	71 (31.7)	
- 15–18	116 (51.8)	
- 19–22	31 (13.8)	
- 23–26	6 (2.7)	
- Unknown	2 (0.9)	
Laboratory Results		
- Glucose (mmol/L)	5.49	99.0± 18.1 (mg/dL)

Variable	Result	Conventional Unit
- Hemoglobin A_{1c} (mmol/mol)	41.0	5.9 ± 0.49 (%)
- Lipid Profile (mmol/L)		
○ Total Cholesterol	3.90	150.8 ± 31.1 (mg/dl)
○ HDL Cholesterol	1.14	44.1 ± 11.3 (mg/dl)
○ LDL Cholesterol	2.03	78.4 ± 25.7 (mg/dl)
○ Triglycerides	1.63	144.1 ± 90.3 (mg/dl)
○ Non HDL Cholesterol[e]	5.9	106.7 ± 29.7 (mg/dl)
- Serum Creatinine (mg/dL)	84.9	0.96 ± 0.17 (mg/dl)
- Estimated Creatinine Clearance (mL/s)[f]	1.90	114.0 ± 27.4 (ml/min)
- Microalbumin Creatinine Ratio		
○ Normal (<3.39 mg/mmol creatinine) [g]	214 (95.5)	
○ Microalbuminia(3.39–33.8mg/mmol creatinine)[h]	10 (4.5)	
SF-36 Health Survey Score		
- Physical Health (0–100)	81 (73–88)	
- Mental Health (0–100)	86 (78–90)	
- Total SF-36 (0–100)	86 (79–91)	
Cognitive Function		
- Mini-Mental State Examination	29 (28–30)	
- Digit Symbol Substitution Test	61 (53–71)	
- Rey Auditory Verbal Learning Test		
○ Sum of the First 4 Trials on List A	30 (26–35)	
○ Short Delay for List A	6 (5–8)	
○ Delayed Recall of List A	6 (5–8)	
○ Delayed Recognition of List A	23 (22–24)	
- Trail Making Tests		
○ Trail A (in seconds)	29 (24–36)	
○ Trail B (in seconds)	72 (57–100)	
- Categorical Verbal Fluency		
○ Score 1 – Sum of Animals	20 (17–24)	
○ Score 2 – Sum of Supermarket Items	25 (21–29)	

Variable	Result	Conventional Unit
○ Score 3 – Sum of Score 1 and Score 2	45 (39–52)	
○ Score 4 – Average of Score 1 and Score 2	23 (20–26)	

Data are means ± SD, n (%) or median (25^{th}–75^{th} percentile).

[a] Mean arterial pressure: [(2*Diastolic) + Systolic]/3

[b] Normal glucose tolerance determined by fasting glucose <5.55 mmol/L (100 mg/dl) and HbA_{1c} <6.5% (47.5 mmol/mol); Impaired fasting glucose determined by fasting glucose between 5.55 mmol/L and 6.94 mmol/L (100 to 126 mg/dl) and HbA_{1c} <6.5% (47.5 mmol/mol); and type 2 diabetes determined by medical history of diagnosis or fasting glucose ≥6.94 mmol/L (126 mg/dl) or HbA1c ≥6.5% (47.5 mmol/mol)

[c] Smoking: if stopped 15 years or more then not a smoker

[d] Self-reported: past medical history self-report of psychological conditions

[e] Non-HDL Cholesterol = Total Cholesterol − HDL Cholesterol

[f] Cockroft-Gault creatinine clearance = ((140-age) × weight (kg))/plasma creatinine × 72 for men (normal 95–145 ml/min)

[g] less than 30 μg/mg creatinine

[h] 30–299 μg/mg creatinine

Table 3

Relationship between Cognitive Function Tests and Hemoglobin A_{1C} in Multivariate Analysis Adjusted for Age, and Age and Education

Association of glycemia with measures of cognitive function in
[A] Model 1: model adjusted for age for full study cohort population
[B] Model 2: model adjusted for age for population excluding type 2 diabetes
[C] Model 3: model adjusted for age and education for full study cohort population

Model 1: Age Adjusted Model (full study cohort)						
Outcome Variable	**R^2**	**Model *P*-value**	**Covariates**	**β (95 CI)**	**Standardized Estimate**	**Covariate *P*-Value**
MMSE	0.06	0.0013	HbA1c	−0.23 (−0.68, 0.22)	−0.07	0.313
			Age	−0.05 (−0.08, −0.02)	−0.21	0.002
DSST	0.13	<0.0001	HbA1c	−5.90 (−9.58, −2.21)	−0.20	0.002
			Age	−0.52 (−0.79, −0.26)	−0.26	0.0001
RAVLT	0.17	<0.0001	HbA1c	−2.44 (−4.00, −0.87)	−0.19	0.002
			Age	−0.28 (−0.39, −0.17)	−0.31	<0.0001
Trail Making B	0.13	<0.0001	HbA1c	15.6 (5.73, 25.6)	0.20	0.002
			Age	1.37 (0.67, 2.08)	0.25	0.0001
CVF	0.04	0.0160	HbA1c	−3.71 (−6.41, −1.01)	−0.18	0.007
			Age	−0.03 (−0.22, 0.16)	−0.02	0.750

Model 2: Age Adjusted Model (study population excluding type 2 diabetes)						
Outcome Variable	**R^2**	**Model *P*-value**	**Covariates**	**β (95 CI)**	**Standardized Estimate**	**Covariate *P*-Value**
MMSE	0.04	0.036	HbA1c	−0.48 (−1.28, 0.31)	−0.09	0.23
			Age	−0.03 (−0.07, 0.003)	−0.14	0.08
DSST	0.09	0.0002	HbA1c	−7.28 (−14.2, −0.41)	−0.16	0.0378
			Age	−0.42 (−0.73, −0.11)	−0.20	0.0075
RAVLT	0.13	<0.0001	HbA1c	−3.51 (−6.4, −0.61)	−0.18	0.0179
			Age	−0.23 (−0.36, −0.10)	−0.26	0.0006
Trail Making B	0.10	0.0001	HbA1c	17.4 (0.29, 34.6)	0.15	0.0463
			Age	1.18 (0.41, 1.95)	0.23	0.0029
CVF	0.02	0.22	HbA1c	−4.07 (−9.11, 0.98)	−0.12	0.11
			Age	−0.02 (−0.25, 0.21)	−0.01	0.86

Model 3: Age and Education Adjusted Model (full study cohort)						
Outcome Variable	**R^2**	**Model *P*-value**	**Covariates**	**β (95 CI)**	**Standardized Estimate**	**Covariate *P*-Value**
MMSE	0.09	<0.0001	HbA1c	−0.098 (−0.55, 0.36)	−0.03	0.673
			Age	−0.06 (−0.09, −0.03)	−0.24	0.001
			Education	0.11 (0.03, 0.19)	0.19	0.003
DSST	0.23	<0.0001	HbA1c	−3.88 (−7.46, −0.31)	−0.13	0.033
			Age	−0.60 (−0.85, −0.35)	−0.29	<0.0001
			Education	1.63 (1.03, 2.23)	0.32	<0.0001
RAVLT	0.24	<0.0001	HbA1c	−1.65 (−3.18, −0.13)	−0.13	0.033
			Age	−0.31 (−0.42, −0.22)	−0.35	<0.0001
			Education	0.58 (0.33, 0.84)	0.27	<0.0001
Trail Making B	0.15	<0.0001	HbA1c	13.2 (3.17, 23.3)	0.17	0.010
			Age	1.51 (0.78, 2.19)	0.27	<0.0001
			Education	−2.08 (−3.96, −0.56)	−0.15	0.016
CVF	0.16	<0.0001	HbA1c	−2.34 (−4.93, 0.25)	−0.11	0.079
			Age	−0.10 (−0.28, 0.08)	−0.07	0.284
			Education	1.27 (0.83, 1.70)	0.36	<0.0001

Table 4

Relationship between Cognitive Function Tests and Hemoglobin A_{1C} in Multivariate Analysis Adjusted for Age, Education and Coronary Risk Factors

Association of glycemia with measures of cognitive function adjusted for (Model 4) age, education, mean arterial pressure, smoking status, body mass index (BMI), non-high density lipoprotein (HDL) Cholesterol, Short Form-36 (SF-36) mental health score, and past medical history of depression in the full study cohort population.

Model 4: Fully Adjusted Model (full study cohort)						
Outcome Variable	**R^2**	**Model *P*-value**	**Covariates**	**β (95 CI)**	**Standardized Estimate**	**Covariate *P*-Value**
MMSE	0.11	<0.0035	HbA_{1c}	−0.15 (−0.63, 0.33)	−0.04	0.539
			Age	−0.06 (−0.09, −0.03)	−0.24	0.001
			Education	0.10 (0.02, 0.18)	0.17	0.014
			Mean Arterial Pressure	0.01 (−0.02, 0.04)	0.06	0.408
			Non-HDL-C	−0.00 (−0.01, −0.01)	−0.00	0.991
			Smoking Status	0.03 (−0.28, 0.34)	0.01	0.849
			BMI	−0.05 (−0.12, 0.02)	−0.09	0.179
			SF-36 Mental	−0.00 (−0.02, 0.01)	−0.03	0.646
			Depression	−0.06 (−0.66, 0.55)	−0.01	0.851
DSST	0.26	<0.0001	HbA_{1c}	−3.60 (−7.31, 0.11)	−0.12	0.057
			Age	−0.66 (−0.92, −0.40)	−0.32	<0.0001
			Education	1.57 (0.94, 2.20)	0.31	<0.0001
			Mean Arterial Pressure	0.13 (−0.08, 0.33)	0.07	0.23
			Non-HDL-C	−0.05 (−0.11, 0.01)	−0.11	0.08
			Smoking Status	0.69 (−1.68, 3.06)	0.04	0.57
			BMI	0.13 (−0.43, 0.68)	0.03	0.66
			SF-36 Mental	0.02 (−0.11, 0.14)	0.02	0.81
			Depression	−2.45 (−7.13, 2.24)	−0.07	0.30
RAVLT	0.27	<0.0001	HbA_{1c}	−1.58 (−3.16, −0.01)	−0.12	0.049
			Age	−0.32 (−0.43, −0.21)	−0.36	<0.0001
			Education	0.60 (0.33, 0.87)	0.28	<0.0001
			Mean Arterial Pressure	0.11 (0.02, 0.20)	0.14	0.018

Model 4: Fully Adjusted Model (full study cohort)

Outcome Variable	R^2	Model *P*-value	Covariates	β (95 CI)	Standardized Estimate	Covariate *P*-Value
			Non-HDL-C	0.00 (−0.02, 0.03)	0.02	0.706
			Smoking Status	−0.04 (−1.05, 0.97)	−0.00	0.941
			BMI	−0.13 (−0.37, 0.11)	−0.06	0.283
			SF-36 Mental	0.03 (−0.03, 0.08)	0.06	0.335
			Depression	−0.41 (−2.40, 1.59)	−0.03	0.688
Trail Making B	0.18	<0.0001	HbA_{1c}	12.0 (1.43, 22.5)	0.15	0.026
			Age	1.63 (0.90, 2.37)	0.29	<0.0001
			Education	−1.79 (−3.57, −0.01)	−0.13	0.049
			Mean Arterial Pressure	0.42 (−0.16, 1.01)	0.09	0.157
			Non-HDL-C	0.13 (−0.03, 0.29)	0.10	0.121
			Smoking Status	−1.50 (−8.22, 5.22)	−0.03	0.661
			BMI	−0.26 (−1.85, 1.32)	−0.02	0.743
			SF-36 Mental	−0.06 (−0.43, 0.30)	−0.02	0.730
			Depression	0.36 (−12.9, 13.6)	0.00	0.957
CVF	0.20	<0.0001	HbA_{1c}	−2.84 (−5.5, −0.16)	−0.14	0.038
			Age	−0.11 (−0.30, 0.07)	−0.08	0.230
			Education	1.44 (0.99, 1.89)	0.41	<0.0001
			Mean Arterial Pressure	0.10 (−0.05, 0.24)	0.08	0.211
			Non-HDL-C	0.01 (−0.03, 0.06)	0.04	0.509
			Smoking Status	−1.62 (−3.3, 0.09)	−0.12	0.063
			BMI	0.16 (−0.24, 0.57)	0.05	0.428
			SF-36 Mental	−0.02 (−0.11, 0.08)	−0.02	0.735
			Depression	−2.44 (−5.81, 0.94)	−0.09	0.156