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TITLE: Body Mass Index, Insulin Sensitivity, and Cognition in Early Type 2 Diabetes: the GRADE study

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AUTHOR CONTRIBUTIONS

JAL contributed to the research design, acquisition, statistical analysis, and interpretation of data, supervision and management of research, and critical review of this manuscript. EK contributed to the research design, statistical analysis and interpretation of data, and drafting of this manuscript. DLS contributed to quality control of neuropsychological data, the supervision and management of research, and the critical review of this manuscript. WV contributed to the acquisition of data, interpretation of data, and critical review of this manuscript. CD contributed to the research design, acquisition of data, interpretation of data and results, supervision and management of research, and the critical review of the manuscript. MEL contributed to the research design, interpretation of data, and critical review of this manuscript. ALC contributed to the acquisition of data, supervision and management of research, and the critical review of this manuscript. RPB contributed to the design, interpretation of data, and critical review of this manuscript. HF contributed to the research design, interpretation of data, and critical review of this manuscript. ES contributed to the acquisition, and interpretation of data, acquisition of funding, supervision and management of research, and critical review of this manuscript. JB contributed to the design of the research, acquisition and interpretation of data, and drafting and critical review of this manuscript.

STUDY IMPORTANCE QUESTIONS

- What is already known about this subject?

  - Persons with type 2 diabetes have worse cognitive performance than persons without type 2 diabetes.
  - Among persons with type 2 diabetes, it is not known whether body mass index and insulin sensitivity are related to cognitive performance.

- What does your study add?

  - This is the first study to explore the association of body mass index and insulin sensitivity with cognitive performance in persons with type 2 diabetes.
  - We found that higher body mass index was related to better cognitive performance, independent of insulin sensitivity, glycemia, and cardiovascular risk factors.

ABSTRACT

Objective: To explore the association of body mass index (BMI) and insulin sensitivity with cognitive performance in persons with type 2 diabetes.

Methods: Cross-sectional analysis of data from the baseline assessment of the Glycemia Reduction Approaches in Diabetes: a comparative effectiveness study (GRADE). We used BMI as a surrogate of adiposity, and the Matsuda index as the measure of insulin sensitivity. Cognitive tests included the Spanish English Verbal Learning Test, the Digit Symbol Substitution test, and the letter and animal fluency test.

Results: 5,018 (99.4%) of 5,047 participants aged 56.7 $\pm$ 10.0 years and 36.4% female completed cognitive assessments. Higher BMI and lower insulin sensitivity were related to better performance in memory and verbal fluency tests. In models including BMI and insulin sensitivity simultaneously, only higher BMI was related to better cognitive performance.

Conclusions: In this study, higher BMI and lower insulin sensitivity, in persons with type 2 diabetes was cross-sectionally associated with better cognitive performance. However, only higher BMI was related to cognitive performance when both BMI and insulin sensitivity were considered simultaneously. The causality and mechanisms for this association need to be determined in future studies.

INTRODUCTION

Persons with type 2 diabetes, representing 11.3% of the adult US population (1), are at higher risk of cognitive impairment (2). However, the determinants of cognitive performance among persons with type 2 diabetes are poorly understood. High body mass index (BMI) and lower insulin sensitivity are two important conditions associated with type 2 diabetes (3), but their association with cognition in persons with type 2 diabetes is not clear. To the best of our knowledge, no study has examined the simultaneous relation of BMI and insulin sensitivity with cognitive performance among persons with type 2 diabetes.

The association between BMI and cognition is controversial (4). Studies in the general population in the midlife age period suggest that higher BMI is related to worse cognitive function cross-sectionally and longitudinally (5), while some studies in persons 65 years and older suggest that higher BMI is related to better cognitive performance (6). Elevated BMI is generally accompanied by lower insulin sensitivity (3), which is associated with worse cognitive performance (7).

Here, we explored the cross-sectional associations of BMI, as a surrogate marker of adiposity, and insulin sensitivity with cognitive performance in persons with type 2 diabetes of approximately 5 years duration in the Glycemia Reduction Approaches in Diabetes: a comparative effectiveness study (GRADE) (8).

METHODS

This is a cross-sectional analysis of the baseline assessment of participants enrolled in the GRADE study who completed cognitive assessments. The GRADE study examined the impact of 4 classes of glucose lowering medications added to metformin therapy (1000 to 2000 mg per day) on glycemic control: glargine insulin, glimepiride (sulfonylurea), liraglutide (Glucagon Like Peptide-1 (GLP-1) receptor agonist), and sitagliptin (Dipeptidyl Peptidase-4 inhibitor [DPP4i]). Eligibility criteria (8) included type 2 diabetes of less than 10 years duration treated with metformin alone, age greater than 30 years at time of diagnosis, baseline hemoglobin A1c (HbA1c) between 6.8 and 8.5% (51 and 69 mmol/mol),

and estimated glomerular filtration rate (eGFR) of more than 30 ml/min at enrollment. Exclusion criteria included any major cardiovascular event in the year prior to recruitment and/or a history of New York Heart Association heart failure stages 3 or 4. Clinic examinations included medical history and medications, along with assessment of body size, blood pressure, laboratory measurements and electrocardiogram. No cognitive screening was conducted as part of the eligibility assessment. The primary outcome of the GRADE study was glycated hemoglobin level, measured quarterly, of 7.0% or higher, and the secondary metabolic outcome was a confirmed glycated hemoglobin level greater than 7.5% (9). The cognitive assessments included in this report were planned a priori as other secondary outcomes and were planned for the GRADE baseline assessment, before randomization, and two follow-up waves during the planned follow-up 4 to 7 years (10). This report focuses on the a priori planned baseline assessment.

Analyses for BMI included 5,038 participants with complete data on BMI and cognition. Analyses for insulin sensitivity included 3,370 subjects with complete data for serum insulin levels derived from baseline OGTT and cognition; those excluded were subjects randomized to insulin glargine, who did not undergo insulin sensitivity testing (11). Insulin measurement in these participants has been deferred due to the difficulty of measuring insulin with immunoassays in persons treated with glargine. There were no significant differences between participants included and excluded in insulin sensitivity analyses (11).

Independent variables: BMI and insulin sensitivity.

BMI was calculated as weight in kilograms (kg) divided by height in meters squared (m^2). Higher BMI indicates greater adiposity. Since all participants had a BMI of 25 kg/m^2 or greater, BMI was dichotomized as with obesity (BMI $\geq$ 30 kg/m^2), or without obesity (BMI < 30 kg/m^2) following National Heart Lung and Blood Institute guidelines (12) for bivariate analyses but was examined as continuous variable in multivariate analyses.

The measure of insulin sensitivity was the Matsuda Index, derived from glucose and insulin values measured during a 75 gm oral glucose tolerance test (13). It is calculated as $10^4/(I_0 \times G_0 \times I_m \times G_m)^{1/2}$, where G_0 and I_0 are the fasting glucose and insulin, and *Gm* and *Im* are the mean glucose and insulin. Higher Matsuda index indicates greater insulin sensitivity (less insulin resistance). For bivariate analyses, we categorized Matsuda Index as high or low using the median as the cutoff, 1.77. The Matsuda Index was winsorized at the median plus (minus) 8.9 times the distance from the median to reduce the effect of outliers. For a normally distributed variable, this results in cutoffs 6 standard deviations above and below the mean. For multivariate analyses, the Matsuda index was examined as a continuous variable. Glucose was measured in EDTA plasma by a hexokinase method on a cobas c501 chemistry analyzer (Roche Diagnostics, Indianapolis, IN). Insulin and C-peptide were measured in EDTA plasma on a cobas e601 immunoassay analyzer using a sandwich immunoassay (Roche Diagnostics).

Dependent variables: cognitive measures

The cognitive battery measured memory (verbal learning) and frontal-executive abilities. Memory refers to the ability to recollect information (14) while frontal-executive abilities refer to those necessary for planning and executing complex tasks, and involve aspects such as psychomotor speed and attention (15). All tests were administered in English or Spanish by centrally trained research staff, according to the participant's reported first language. The measure of memory was the Spanish English Verbal Learning Test (SEVLT) (16). The SEVLT consists of recalling a list of 15 words in 3 trials of immediate recall and 1 trial after a distractor list. For the SEVLT, we examined two outcomes, the sum of the number of words recalled in the first 3 trials (immediate recall), and the score of the 4th trial after the distractor list (delayed recall). The tests of frontal-executive abilities were the total score in the Digit Symbol Substitution Test (DSST) (17) and number of words generated in the animal (18) and letter (19) fluency tests. The DSST is a test in which participants try to match numbers to symbols in 90 seconds. The total number of correct answers is reported. The animal fluency test asks participants to name as

many animals as they can in one minute. The letter fluency test asks participants for as many words as possible that begin with the letter F in English (P in Spanish) in one minute. The total number of correct words is reported for the fluency tests. For all cognitive tests, a higher score indicates better performance.

Covariates

We included as covariates factors that have been reported to be associated with cognitive performance, obesity, and insulin sensitivity. Demographic covariates included age in years, male or female sex, ethnic and racial group, and education (less than high school, high school, some college, college, and graduate school). Diabetes covariates included hemoglobin A1c (HbA1c) at time of randomization and diabetes duration in years. Other factors previously reported as predictive of cognitive performance included the Framingham Risk Score (20), depression, stroke history, and alcohol use. The Framingham Risk Score is derived from a sex specific Cox proportional hazards model with the following covariates: age (years), total cholesterol (mg/dL), HDL cholesterol (mg/dL), systolic blood pressure (mmHg), antihypertensive medication use, current smoking, and diabetes status. Depression was ascertained with a positive response to the question “are you depressed?” or use of anti-depression medications. Stroke history and alcohol use were ascertained by self-report.

Statistical analysis:

For bivariate analyses, BMI and Matsuda Index subgroups were defined prior to analysis as BMI greater than or equal to 30 kg/m^2, and Matsuda Index less than 1.77, respectively. Continuous variables were summarized across groups using means ± standard deviations and medians and interquartile ranges for variables with skewed distributions, while discrete variables were summarized using cell counts and column percentages. The Matsuda Index included some extreme outliers. To reduce the influence of outliers on analyses, this variable was winsorized using cutoffs of approximately 0.203 and 9.675. (i.e., values above or below specified cutoffs were replaced by cutoffs). The number

of winsorized values is 23 (1%). Comparisons between baseline characteristics and BMI/Matsuda categories was assessed using χ^2 test of independence for discrete variables and Welch's Two Sample t-test for continuous variables.

We assessed the possibility of nonlinear associations of BMI and Matsuda index with cognitive measures using graphical analysis of the data first before determining whether to use generalized additive models to model nonlinear relationships. All relationships were found to be linear and not appropriate to further explore nonlinear associations.

Least-squares regression model output for the main risk factors (BMI and Matsuda) for each of the cognitive responses (SEVLT, DSST, WF-letter and WF-animal fluency) are shown in Tables 2, 3, 5, and 6. The cognitive variables, BMI and Matsuda are included as continuous variables in all models. The covariates included in the models were chosen a priori. The four separate models in Tables 2, 3 5, and 6 are 1) unadjusted, 2) adjusted for age, race/ethnicity, sex, education, 3) model 2 plus HbA1c at baseline and duration of diabetes diagnosis and 4) model 3 plus Framingham Risk Score, depression, stroke history, and alcohol use.

The p values in Figure 1A are from a least-squares regression of each of the responses on BMI categories adjusted for age, race/ethnicity, sex, education, HbA1c, duration of diabetes diagnosis, Framingham Risk Score, depression, stroke history, alcohol use, and Matsuda Index. The means and 95% confidence intervals are least-squares means (predicted marginal means) for cognitive test score comparisons by BMI adjusted for age, race/ethnicity, sex, education, HbA1c, duration of diabetes diagnosis, Framingham Risk Score, depression, stroke history, alcohol use, and Matsuda Index. The p values in Figure 1B are from a least-squares regression of each of the responses on Matsuda categories adjusted for age, race/ethnicity, sex, education, HbA1c, duration of diabetes diagnosis, Framingham Risk Score, depression, stroke history, alcohol use, and BMI. The means and 95% confidence intervals are least-squares means for cognitive test score comparisons by Matsuda Index adjusted for age, race/ethnicity, sex, education, HbA1c, duration of diabetes diagnosis, Framingham Risk Score, depression, stroke history, alcohol use, and BMI.

Because of previously reported effect modification by age in the association between adiposity measures and cognition (5), we explored interaction terms for age in all associations adjusted for sex and education. We also explored interactions of BMI and Matsuda index, and BMI and ethnic and racial groups adjusted for age, sex, and education. Given that the sample with insulin sensitivity data was smaller than the sample with BMI, we conducted sensitivity analyses of the association of BMI with cognitive measures restricted to the sample with insulin sensitivity data.

RESULTS

Among the 5,047 participants recruited into GRADE, 5,018 (99.4%) completed cognitive assessments. Their mean age was 56.7 ± 10.0 years, 36.4% were women, 52.9% were Non-Hispanic White, 19.0% Non-Hispanic Black, 18.6% were Hispanic, 3.6% were Asian, 2.8% were American Indian or Alaska Native, and 0.6% were Hawaiian or Pacific Islanders. The mean type 2 diabetes duration was 4.0 ± 2.7 years, and the mean HbA1c measured at baseline was 7.5 ± 0.5% (58 ± 3.1 mmol/mol).

Body mass index and cognition

Table 1 shows the baseline characteristics and cognitive scores of the GRADE cohort categorized by BMI status (with obesity vs. without obesity). Of the 5,038 participants with full data, 3,592 (71.3%) had a BMI ≥ 30. As compared to individuals without obesity, those with obesity were younger, were more likely to be female, to be White, were less likely to be current smokers, were less likely to drink alcohol, and to have depression. They also had shorter known duration of diabetes. They had more hypertension, but their Framingham Risk score was lower. All cognitive test scores were higher in the obesity group compared with those without obesity.

Table 2 shows the results of regression models relating BMI to cognitive performance. In the model adjusted for demographics and education (model 2), higher BMI was associated with higher scores in

immediate recall, delayed recall and animal fluency. There were no significant associations between BMI and DSST and letter fluency scores. These findings persisted in the fully adjusted model, which included measures of glycemia and cardiovascular risk. We conducted sensitivity analyses in the subsample with insulin sensitivity data and found that the associations between higher BMI with higher scores in immediate recall, delayed recall and animal fluency were robust, but the new significant associations between of higher BMI with higher scores in DSST and letter fluency appeared (Table 3).

Insulin sensitivity

Table 4 shows the baseline characteristics by Matsuda index categories. Persons with higher Matsuda index (greater insulin sensitivity, less insulin resistance), were older, less likely to be white, more likely to be current smokers, less likely to report depression, had longer diabetes duration, had a lower HbA1c at baseline, and lower BMI.

Table 5 shows the relation of the Matsuda index with cognitive performance. Higher Matsuda index (greater insulin sensitivity) was related to lower performance in immediate recall, delayed recall, and animal fluency in the model adjusted for demographics and education. These associations persisted in the fully adjusted model. Higher insulin sensitivity was related to lower performance in the DSST in the crude model; this association was attenuated and became non-significant in the models adjusting for demographics (model 2) and glycemia (model 3) but became significant in the fully adjusted model (model 4).

Adiposity and insulin sensitivity examined simultaneously

Table 6 shows the regression coefficients relating BMI and the Matsuda index tested simultaneously to cognitive performance in all models. In the model adjusted for demographics (model 2), the relation of BMI with better SEVLT immediate recall and animal fluency persisted, but the relation with better SEVLT delayed recall was no longer significant. These associations for BMI persisted in the fully adjusted model. None of the associations for the Matsuda Index were significant in the adjusted models. Figure 1 shows

a comparison of fully adjusted means of cognitive test scores between categories of BMI and Matsuda index. Persons with BMI ≥ 30 had significantly higher scores in SEVLT immediate recall, delayed recall, DSST and animal fluency tests. Persons with Matsuda Index ≥ 1.77 had consistently higher scores for the cognitive tests, but these results were not significant ($p>0.05$).

Lastly, for the association between BMI and cognitive tests, we explored effect modification by age, racial and ethnic group, and Matsuda index. The interaction terms for age with BMI and Matsuda Index with BMI were not significant (all had $p > 0.05$). Suggesting that the association between BMI and cognitive performance in this sample was not modified by age or insulin sensitivity. Significant Interactions with BMI and race/ethnicity were found for SEVLT delayed recall ($p = 0.03$), DSST score ($p < 0.0001$), and animal fluency ($p = 0.01$). For the SEVLT delayed recall we found that Non-Hispanic Blacks have a 0.0332 increase in mean SEVLT delayed recall for a unit increase in BMI compared to Non-Hispanic Whites ($p = 0.008$) and a 0.0366 increase in mean SEVLT delayed recall for a unit increase in BMI compared to Hispanics ($p = 0.024$). Both Hispanics and non-Hispanic Blacks had an increase in mean DSST for a unit increase in BMI (0.268, $p < 0.001$ and 0.219, $p = 0.0002$) compared to Non-Hispanic Whites, respectively. For the animal fluency test, Hispanics had a 0.0712 mean increase in score for a unit increase in BMI compared to Non-Hispanic Whites ($p = 0.014$).

DISCUSSION

In this cross-sectional exploratory analysis of persons with type 2 diabetes of relatively short duration, we found that higher BMI was associated with better performance on tests of recall (memory) and verbal fluency. We also found that higher insulin sensitivity was related to worse performance in these cognitive domains. After simultaneously considering the association of BMI and insulin sensitivity with cognition, only the findings for BMI persisted, suggesting that the association between higher BMI and better cognitive performance was independent of insulin sensitivity. These findings were robust in models adjusting for factors related to cognition such as age, sex, and ethnic and racial group,

glycemia and cardiovascular risk factors. To the best of our knowledge, this is the first study to explore the association of BMI and insulin sensitivity with cognitive performance among persons with type 2 diabetes. Given that our main finding is that higher BMI is related to better cognitive performance independent of insulin sensitivity, glycemia, and vascular risk profile, we focus our discussion on the association between BMI and cognitive performance, with the caveat that there is a dearth of studies examining this association in persons with type 2 diabetes.

Greater BMI is related to adverse cerebrovascular outcomes including stroke and cerebral microvascular disease (21), and thus is expected to be related to worse cognition. However, the association between BMI and cognitive performance is controversial. Most studies examining the association of BMI with cognitive performance in adults have found that elevated BMI in middle age is related to worse cognitive performance in later age (5, 22, 23) but the evidence in older adults is mixed, with some studies showing worse cognitive performance in relation to higher BMI (24), and other studies finding an inverse association (5). This paradox does not seem to be explained by the type of adiposity measure used (e.g., BMI vs. measures of central obesity). For example, an analysis in the Cardiovascular Health Study in persons with and without diabetes aged 65 years and older compared the association of multiple measures of adiposity, including BMI, waist circumference, waist to hip ratio, and fat mass measured by bioelectrical impedance, with cognitive performance. It found that BMI, waist circumference, waist to hip ratio, and fat mass, were related to better cognitive performance cross-sectionally and longitudinally (6), consistent with our finding in a younger sample with type 2 diabetes.

We found ethnic differences in the relation of higher BMI with improved scores in the SEVLT total recall, DSST, and the animal fluency test. In general, these associations were found to be stronger in Hispanics or non-Hispanic Blacks compared with Non-Hispanic Whites. This finding from exploratory analyses is hypothesis generating, and we can only speculate about the mechanisms. It is possible that the accuracy of BMI as a measure of adiposity varies by ethnic group (25), and this can be only overcome with direct measurement of fat depots, such as with the use of computed tomography (26).

Our study is cross-sectional, and we cannot make inferences about causality. However, there may be plausible mechanisms that could explain the association of higher BMI with better cognitive performance. The adipokine leptin, which increases with higher BMI, has been hypothesized to be neuroprotective (27). The Framingham Heart Study reported that higher leptin levels were associated with a lower risk of cognitive impairment and higher brain volume, a surrogate marker of brain health (28). Another factor that increases with BMI, uric acid, has also been hypothesized to be neuroprotective (29). We do not have the data to test these potential mechanisms.

We must also consider potential factors that threaten the validity of our findings, including confounding, bias, and chance. In terms of confounding, our results were robust across models adjusting for demographic, diabetes related, and cardiovascular confounders. It seems unlikely that our results were due to confounding, although residual or unmeasured confounding is possible. In terms of bias, it seems unlikely that cognitive testing was conducted differently according to BMI or Matsuda index levels. It is also unlikely that persons with dementia, who may have weight loss (30), were part of the study because of the relatively young age of the cohort. The Matsuda index has a lower correlation with the euglycemic insulin clamp in persons with diabetes compared with persons with normal glucose tolerance and impaired glucose tolerance, which is likely due to a decrease in insulin secretion among persons with diabetes (13). This is a source of measurement bias that could have led to regression dilution bias, that is, an underestimation of the association between the Matsuda index and the cognitive tests. Our results for BMI in the larger GRADE cohort with BMI and cognitive data were similar in the smaller sample with insulin sensitivity data. Thus, selection bias seems an unlikely explanation for our findings. It is possible that our results are due to chance, particularly in a relatively large sample such as the one used for this report, but the results were robust in different analyses and models. Thus, chance seems unlikely.

There are multiple strengths in this analysis. The cohort is large, well-phenotyped, and diverse. The tests of cognition are widely used and standardized. The known duration of type 2 diabetes was less than 5 years on average, so that the effects of long duration hyperglycemia probably did not affect our

analyses. In fact, glycemia was not associated with cognitive performance in a cross-sectional analysis of baseline data from this cohort (31). Also, the prevalence of clinical cardiac, cerebral, and renal diseases, which can confound the assessment of cognitive function, was low.

Limitations of the study include a cross-sectional design, such that the directionality of association of obesity and insulin sensitivity with measures of cognitive function cannot be established. It is possible that the sample is relatively homogenous in terms of insulin sensitivity because all participants have type 2 diabetes, limiting the study's ability to find an association between insulin sensitivity and cognitive performance. In addition, the great majority of the sample was in the overweight and obesity BMI range and comparisons with persons with normal and underweight categories could not be made. Only 233 subjects had a BMI of less than 25 k/m^2. A major limitation of BMI is the assumption that excess weight is reflecting excess total body fat, without consideration for where in the body the excess fat is located, and without consideration for the effect that reduced or excess lean mass has on the interpretation of BMI. BMI may be a suboptimal marker of adiposity in the elderly (32), who are at highest risk of cognitive impairment. The location of fat depots, such as visceral fat, has been demonstrated to have greater importance in its relation to cardiovascular disease (26, 33), which may be an important mediator of cognitive outcomes.

Longitudinal analyses in the GRADE study will allow to assess whether interventions that affect BMI and insulin sensitivity, can affect cognitive function.

CONCLUSION.

In conclusion, higher BMI is related to better cognitive performance among persons with type 2 diabetes of relatively short duration, independent of insulin sensitivity. While lower insulin sensitivity as measured with the Matsuda Index was related to better cognitive performance, this association disappeared when BMI was included in statistical models. These results should be considered hypothesis generating given the cross-sectional design and the exploratory nature of our analyses.

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Table 1. Comparison of characteristics between body mass index (BMI) categories. Continuous variables were compared using T-tests and categorical variables using chi-squared.

	BMI < 30	BMI ≥ 30	p-value
Number of participants	1,446	3,592[1]	
Age ± standard deviation in years	59.0±9.9	56.4±9.9[2]	<0.001[6]
Female	461 (31.9%)	1,375 (38.3%)[3]	<0.001[7]
Race/ethnicity			<0.001[8]
White	679 (47.4%)	2,038 (57.2%)[4]	
Asian	113 (7.9%)	70 (2.0%)	
Black	270 (18.9%)	270 (18.9%)	
Hispanic	323 (22.6%)	709 (19.9%)	
Native American	22 (1.5%)	98 (2.7%)	
Other	25 (1.7%)	46 (1.3%)	
Highest level of school achieved			<0.001[8]
Less than high school	136 (9.4%)	228 (6.3%)	
High school/GED	292 (20.2%)	746 (20.8%)	
Some college	369 (25.5%)	1,091 (30.4%)	
College	376 (26.0%)	955 (26.6%)	
Graduate School	273 (18.9%)	571 (15.9%)[4]	
Smoking			<0.001[8]
Never	803 (55.5%)	1,928 (53.7%)	
Past	411 (28.4%)	1,202 (33.5%)	
Current	232 (16.0%)	462 (12.9%)[4]	
Frequency of alcohol use			<0.001[8]
Never	489 (33.8%)	1,185 (33.0%)	
Occasionally	697 (48.2%)	1,920 (53.5%)	
Weekly	176 (12.2%)	385 (10.7%)	

	BMI < 30	BMI ≥ 30	p-value
Daily	84 (5.8%)	102 (2.8%)[4]	
Depression diagnosis or medication[9]	147 (10.2%)	525 (14.6%)[3]	<0.001[7]
Diabetes duration (years)	4.5±2.9	3.9±2.7[2]	<0.001[6]
Hemoglobin A1c (%)	7.4±0.5	7.5±0.5[2]	<0.001[6]
Hemoglobin A1c (mmol/mol)	57.9±5.3	58.5±5.3	<0.001[6]
Myocardial infarction history[11]	84 (5.8%)	167 (4.6%)[3]	0.101[7]
Stroke history[11]	33 (2.3%)	63 (1.8%)[3]	0.260[7]
Systolic blood pressure (mmHg)	126.9±14.9	128.9±14.6[2]	<0.001[6]
Diastolic blood pressure (mmHg)	75.6±9.5	78.0±9.9[2]	<0.001[6]
Hypertension	931 (64.4%)	2,732 (76.1%)[3]	<0.001[7]
Hyperlipidemia	1,106 (76.5%)	2,738 (76.2%)[3]	0.872[7]
Total cholesterol (mg/dL)	164.4±39.2	163.6±37.1[2]	0.477[6]
High density lipoprotein (mg/dL)	45.7±11.7	42.5±9.9[2]	<0.001[6]
Low density lipoprotein (mg/dL)	91.5±32.9	90.2±31.2[2]	0.177[6]
Framingham Risk Score[10]	24.4±15.9	23.3±15.2[2]	0.018[6]
Matsuda (1/uU*mg/dL^2)	3.1±1.8	1.8±1.1[2]	<0.001[6]
SEVLT immediate recall score	24.4±5.8	25.6±5.9[2]	<0.001[6]
SEVLT delayed score	9.0±2.6	9.5±2.7[2]	<0.001[6]
DSST score	43.9±13.7	46.9±13.8[2]	<0.001[6]
WF-Letter score	12.1±4.5	12.5±4.4[2]	0.011[6]
WF-Animal score	18.4±5.3	19.6±5.4[2]	<0.001[6]

[1]Number of observations; [2]Mean and standard deviation; [3]Cell count and column %; [4]Count and column %; [5]Median and quartiles; [6]Welch Two Sample t-test; [7]Pearson's Chi-squared test with Yates' continuity correction; [8]Pearson's Chi-squared test; [9]Question implemented in October 2015. [10]Framingham General Cardiovascular Risk Score for estimating the 10-year cardiovascular risk. The score is derived from a sex specific Cox proportional hazards model with the following covariates: age (years), total cholesterol (mg/dL), HDL cholesterol (mg/dL), systolic blood pressure (mmHg), antihypertensive medication use, current smoking, and diabetes status. [11]Any major cardiovascular event in the past year, including history of myocardial infarction and stroke, is an exclusion criteria in the GRADE study.

Table 2. Regression coefficient (ß) and p values from least squares regression models for the association of body mass index (BMI) with performance in tests of cognitive function. Model 1 is the unadjusted model; Model 2 adds adjustment for age, race/ethnicity, sex, education; Model 3 adds HbA1c at baseline and duration of diabetes diagnosis; and Model 4 further adjusts for the Framingham Risk Score, depression, stroke history, and alcohol use

	Model 1		Model 2		Model 3		Model 4	
	ß	p	ß	p	ß	p	ß	p
Spanish English Verbal Learning Test immediate recall								
Number	5007		4966		4965		4953	
BMI	0.122	<0.001	0.0381	<0.001	0.0387	<0.001	0.0446	<0.001
Spanish English Verbal Learning Test delayed recall								
Number	5005		4964		4963		4951	
BMI	0.0525	<0.001	0.0161	0.002	0.0161	0.002	0.0185	<0.001
Digit Symbol Substitution Test								
Number	5003		4962		4961		4949	
BMI	0.2533	<0.001	0.0304	0.215	0.0298	0.226	0.0468	0.058
Letter Fluency								
Number	5009		4968		4967		4955	
BMI	0.0328	<0.001	0.0029	0.751	0.0041	0.655	0.0089	0.338
Animal Fluency								
Number	5009		4968		4967		4955	
BMI	0.1027	<0.001	0.0497	<0.001	0.0502	<0.001	0.0558	<0.001

Table 3. Regression coefficient (ß) and p values from least squares regression models for the association of body mass index (BMI) with performance in tests of cognitive function restricted to those with insulin sensitivity data. Model 1 is the unadjusted model; Model 2 adds adjustment for age, race/ethnicity, sex, education; Model 3 adds HbA1c at baseline and duration of diabetes diagnosis; and Model 4 further adjusts for the Framingham Risk Score, depression, stroke history, and alcohol use

	Model 1		Model 2		Model 3		Model 4	
	ß	p	ß	p	ß	p	ß	p
Spanish English Verbal Learning Test immediate recall								
Number	3362		3362		3360		3354	
BMI	0.124	<0.001	0.0593	<0.001	0.0592	<0.001	0.0641	<0.001
Spanish English Verbal Learning Test delayed recall								
Number	3360		3360		3358		3352	
BMI	0.0515	<0.001	0.0224	<0.001	0.0222	<0.001	0.0238	<0.001
Digit Symbol Substitution Test								
Number	3361		3361		3359		3353	
BMI	0.289	<0.001	0.115	<0.001	0.1078	<0.001	0.1207	<0.001
Letter Fluency								
Number	3364		3364		3362		3356	
BMI	0.0432	<0.001	0.0234	0.037	0.0242	0.031	0.0274	0.015
Animal Fluency								
Number	3364		3364		3362		3356	
BMI	0.1027	<0.001	0.0497	<0.001	0.0502	<0.001	0.0558	<0.001

Table 4: Comparison of characteristics between Matsuda index categories. Continuous variables were compared using T-tests and categorical variables using chi-squared.

	< 1.77	≥ 1.77	p-value
Number of participants	1,683 (49.9%)[0]	1,687[1] (50.1%)[0]	
Age ± standard deviation in years	56.4 ± 10.2	58.0 ± 9.72	<0.0016
Female	620 (36.8%)	590 (35.0%)[3]	0.274[7]
Race/ethnicity			<0.001[8]
White	1,190 (70.7%)	1,059 (62.8%)	
Asian/Hawaiian/Pacific Islander	64 (3.8%)	93 (5.5%)	
Black or African-American	239 (14.2%)	367 (21.8%)	
American Indian/Alaska Native	70 (4.2%)	33 (2.0%)	
Other/unknown	120 (7.1%)	135 (8.0%)	
Highest level of school achieved			0.037[8]
Less than high school	103 (6.1%)	145 (8.6%)	
High school/GED	360 (21.4%)	351 (20.8%)	
Some college	495 (29.4%)	445 (26.4%)	
College	439 (26.1%)	449 (26.6%)	
Graduate School	286 (17.0%)	297 (17.6%)[4]	
Smoking			<0.001[8]
Never	881 (52.3%)	952 (56.4%)	
Past	587 (34.9%)	483 (28.6%)	
Current	215 (12.8%)	252 (14.9%)[4]	
Frequency of alcohol use			0.051[8]
Never	584 (34.7%)	543 (32.2%)	
Occasionally	875 (52.0%)	870 (51.6%)	
Weekly	171 (10.2%)	197 (11.7%)	
Daily	53 (3.1%)	77 (4.6%)[4]	

	< 1.77	≥ 1.77	p-value
Depression diagnosis or medication	272 (16.2%)	162 (9.6%)[3]	<0.001[7]
Diabetes duration (years)	3.8 ± 2.7	4.3 ± 2.82	<0.001[6]
Hemoglobin A1c (%)	7.5±0.5	7.5±0.5[2]	<0.001[6]
Hemoglobin A1c (mmol/mol)	58.7±5.3	58.1±5.2	<0.001[6]
Body Mass Index (kg/m^2)	36.7±6.6	31.6±5.7[2]	<0.001[6]
Myocardial infarction history[11]	84 (5.0%)	81 (4.8%)[3]	0.861[7]
Stroke history[11]	32 (1.9%)	33 (2.0%)[3]	1.000[7]
Systolic BP (mmHg)	128.6±14.3	127.8±15.0[2]	0.130[6]
Diastolic BP (mmHg)	77.9±9.8	76.5±9.7[2]	<0.001[6]
Hypertension	1,308 (77.7%)	1,125 (66.7%)[3]	<0.001[7]
Hyperlipidemia	1,643 (97.6%)	1,605 (95.1%)[3]	<0.001[7]
Total cholesterol (mg/dL)	163.3 ±37.4	163.3 ±37.3[2]	0.993[6]
High density lipoprotein (mg/dL)	40.8 ±9.2	46.0 ±11.3[2]	<0.001[6]
Low density lipoprotein (mg/dL)	88.2 ±31.1	91.4 ±31.4[2]	0.003[6]
Framingham Risk Score[10]	24.2 ±15.9	23.1 ±15.2[2]	0.051[6]
SEVLT sum score	25.7 ±6.0	24.9 ±5.9[2]	<0.001[6]
SEVLT last score	9.5 ±2.6	9.2 ±2.7[2]	<0.001[6]
DSST score	47.2 ±13.7	44.9 ±13.8[2]	<0.001[6]
WF-Letter Total Correct	12.5 ±4.3	12.3 ±4.5[2]	0.284[6]
WF-Animal Total Correct	19.7 ±5.2	18.8 ±5.5[2]	<0.001[6]

[0]Row percentage. [1]Number of observations; [2]Mean and standard deviation; [3]Cell count and column %; [4]Count and column %; [5]Median and quartiles; [6]Welch Two Sample t-test; [7]Pearson's Chi-squared test with Yates' continuity correction; [8]Pearson's Chi-squared test; [9]Question implemented in October 2015. [10]Framingham General Cardiovascular Risk Score for estimating the 10-year cardiovascular risk. The score is derived from a sex specific Cox proportional hazards model with the following covariates: age, total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medication use, current smoking, and diabetes status. [11]Any major cardiovascular event in the past year, including history of myocardial infarction and stroke is an exclusion criteria in the GRADE study.

Table 5. Regression coefficient (ß) and p values from least squares regression models for the association of the Matsuda index with performance in tests of cognitive function. Model 1 is the unadjusted model; Model 2 adds adjustment for age, race/ethnicity, sex, education; Model 3 adds HbA1c at baseline and duration of diabetes diagnosis; and Model 4 further adjusts for the Framingham Risk Score, depression, stroke history, and alcohol use

	Model 1		Model 2		Model 3		Model 4	
	ß	p	ß	p	ß	p	ß	p
Spanish English Verbal Learning Test immediate recall								
Number	3367		3341		3340		3333	
Matsuda	-0.3541	<0.001	-0.1342	0.035	-0.1393	0.033	-0.1672	0.010
Spanish English Verbal Learning Test delayed recall								
Number	3365		3339		3338		3331	
Matsuda	-0.165	<0.001	-0.0737	0.011	-0.0744	0.011	-0.085	0.004
Digit Symbol Substitution Test								
Number	3366		3340		3339		3332	
Matsuda	-0.9569	<0.001	-0.2432	0.074	-0.213	0.120	-0.3222	0.019
Letter Fluency								
Number	3369		3343		3342		3335	
Matsuda	-0.0419	0.425	0.0478	0.347	0.0453	0.375	0.020	0.699
Animal Fluency								
Number	3369		3343		3342		3335	
Matsuda	-0.331	<0.001	-0.1195	0.042	-0.1157	0.050	0.1409	0.018

Table 6. Regression coefficient and p values from least squares regression models for the association of BMI and the Matsuda index, tested together, with performance in tests of cognitive function Model 1 is the unadjusted model; Model 2 adds adjustment for age, race/ethnicity, sex, education; Model 3 adds HbA1c at baseline and duration of diabetes diagnosis; and Model 4 further adjusts for the Framingham Risk Score, depression, stroke history, and alcohol use

	Model 1		Model 2		Model 3		Model 4	
	ß	p	ß	p	ß	p	ß	p
Spanish English Verbal Learning test immediate recall								
Number	3362		3336		3335		3329	
BMI	0.111	<0.001	0.0317	0.044	0.0319	0.043	0.0367	0.019
Matsuda	-0.1422	0.066	-0.0798	0.252	-0.082	0.240	-0.1048	0.136
Spanish English Verbal Learning test delayed recall								
Number	3360		3334		3333		3327	
BMI	0.0447	<0.001	0.0115	0.108	0.0115	0.107	0.0132	0.065
Matsuda	-0.0785	0.023	-0.0524	0.098	-0.0531	0.095	-0.0609	0.057
Digit Symbol Substitution Test								
Number	3361		3335		3334		3328	
BMI	0.2402	<0.001	0.0414	0.219	0.0384	0.254	0.0485	0.148
Matsuda	-0.5063	0.005	-0.1837	0.218	-0.1596	0.286	-0.2478	0.099
Letter Fluency								
Number	3364		3338		3337		3331	
BMI	0.0471	<0.001	0.0176	0.163	0.018	0.152	0.0198	0.116
Matsuda	0.0472	0.414	0.0771	0.166	0.0749	0.180	0.0538	0.340
Animal Fluency								
Number	3364		3338		3337		3331	
BMI	0.1072	<0.001	0.0566	<0.001	0.0566	<0.001	0.0613	<0.001
Matsuda	-0.1285	0.064	-0.0231	0.719	-0.0203	0.752	-0.0375	0.562

Figure 1. A: Comparison of adjusted means and 95% confidence intervals of cognitive test scores for body mass index (BMI) <30 and ≥ 30 k/m^2. Means and P values are adjusted for age, race/ethnicity, sex, education, hemoglobin A1c, duration of diabetes diagnosis, Framingham Risk Score, depression, stroke history, alcohol use, and Matsuda Index. The P values are for comparisons between BMI groups.
B: Comparison of adjusted means and 95% confidence intervals of cognitive test scores for Matsuda index (M) <1.77 and ≥ 1.77 $1/uU*mg/dL^2$. Means and P values are adjusted for age, race/ethnicity, sex, education, hemoglobin A1c, duration of diabetes diagnosis, Framingham Risk Score, depression, stroke history, alcohol use, and BMI. The P values are for comparisons between Matsuda index groups.
The cognitive tests are the Spanish English Verbal Learning Test immediate recall (SEVLT IR) SEVL delayed recall (SEVLT DR), Digit Symbol Substitution Test (DSST), Letter Fluency (WFT Letter), and Animal Fluency (WFT Animal).