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Association of Glycemia, Lipids, and Blood Pressure With Cognitive Performance in People With Type 2 Diabetes in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

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OBJECTIVE

Type 2 diabetes is a risk factor for cognitive impairment. We examined the relation of glycemia, lipids, blood pressure (BP), hypertension history, and statin use with cognition in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE).

RESEARCH DESIGN AND METHODS

Cross-sectional analyses from GRADE at baseline examined the association of glycemia (hemoglobin A_{1c} [HbA_{1c}]), LDL, systolic BP (SBP) and diastolic BP (DBP), hypertension history, and statin use with cognition assessed by the Spanish English Verbal Learning Test, letter and animal fluency tests, and Digit Symbol Substitution Test (DSST).

RESULTS

Among 5,047 GRADE participants, 5,018 (99.4%) completed cognitive assessments. Their mean age was 56.7 ± 10.0 years, and 36.4% were women. Mean diabetes duration was 4.0 ± 2.7 years. HbA_{1c} was not related to cognition. Higher LDL was related to modestly worse DSST scores, whereas statin use was related to modestly better DSST scores. SBP between 120 and 139 mmHg and DBP between 80 and 89 mmHg were related to modestly better DSST scores. Hypertension history was not related to cognition.

CONCLUSIONS

In people with type 2 diabetes of a mean duration of <5 years, lower LDL and statin use were related to modestly better executive cognitive function. SBP levels in the range of 120–139 mmHg and DBP levels in the range of 80–89 mmHg, but not lower levels, were related to modestly better executive function. These differences may not be clinically significant.

People with type 2 diabetes have been consistently shown to have a higher risk of cognitive impairment, ranging from mild cognitive impairment to dementia, including amnestic and nonamnestic cognitive domains, compared with people without

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**A complete list of the GRADE Research Group can be found in the supplementary material online.*

diabetes (1). However, the correlates of cognitive performance among people with type 2 diabetes requires further study. The Diabetes Control and Complications Trial (DCCT) examined cognitive performance in people with type 1 diabetes with a mean age of ~46 years and a diabetes duration of 24 years (2). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study provided information on cognitive performance in people with advanced type 2 diabetes, with a mean duration of 10 years and a mean age of 62.5 years (3). The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) provides a unique opportunity to study cognitive performance in people with type 2 diabetes of relatively short duration.

GRADE is a clinical trial of >5,000 adults ≥30 years of age with diabetes of <10 years' duration (4,5). Participants in GRADE are randomized to one of four classes of antihyperglycemic agents added to metformin therapy (1,000–2,000 mg/day) on glycemic control: insulin glargine, a dipeptidyl peptidase 4 inhibitor (sitagliptin), a sulfonylurea (glimepiride), and a glucagon-like peptide 1 receptor agonist (liraglutide). Our main goal was to examine the association of parameters usually followed by clinicians for type 2 diabetes control with cognitive performance among people with type 2 diabetes of relatively short duration.

In the current study, we report cognitive performance in the GRADE cohort at baseline in relation to type 2 diabetes control parameters, namely glycemia, lipids, and blood pressure (BP). We hypothesized that better glycemic, lipid, and BP control are related to better cognitive performance among people with diabetes of ~4 years mean duration. In addition, owing to concerns of cognitive impairment related to HMG-CoA reductase inhibitors (statins) (6), which are frequently used by people with type 2 diabetes to control dyslipidemia, we compared cognitive performance between those reporting and not reporting statin use.

RESEARCH DESIGN AND METHODS

Design

This is a cross-sectional analysis of the baseline assessment of participants enrolled in GRADE who completed cognitive assessments. Eligibility criteria include <10 years type 2 diabetes duration treated with metformin alone, age >30 years at time of diagnosis, baseline hemoglobin A_{1c} (HbA_{1c}) between 6.8% and 8.5%, and estimated glomerular filtration rate >30 mL/min/1.73 m^2 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 stage 3 or 4. Clinical examination included medical history and medications along with a body size assessment, BP and laboratory measurements, and an electrocardiogram. No cognitive screening was conducted as part of the eligibility assessment.

Study Participants

A total of 5,047 participants were recruited in GRADE across 36 clinical centers and 9 additional subsites in the U.S. (5), of which 5,018 (99.4%) completed at least one of the cognitive assessments.

Cognitive Assessments

The cognitive battery measured memory (verbal learning) and frontal-executive abilities. Memory refers to the ability to recall information (7) while frontal-executive abilities refer to those necessary for planning and executing complex tasks and involve aspects such as psychomotor speed and attention (8). These cognitive domains are important for people with type 2 diabetes because they might affect the task of following a complex treatment regimen. 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) (9). The SEVLT consists of recalling a list of 15 words in three trials of immediate recall and one trial after a distractor list. For the SEVLT, we examined two outcomes: the sum of the number of words recalled in the first three trials (immediate recall) and the score of the fourth trial after the distractor list (delayed recall). The tests of frontal-executive abilities were the total score in the Digit Symbol Substitution Test (DSST) (10) and number of words generated in the animal (11) and letter (12) fluency tests. In the DSST, participants try to match numbers to symbols in 90 s. The total number of correct answers is reported. The animal fluency test asks participants to name as many animals as they can in 1 min. The letter fluency test asks participants for as many words as possible with the letter F in English (P in Spanish) in 1 min. The total number of correct words is reported for the fluency tests. For all cognitive tests, a higher score indicated better cognitive performance.

Demographic Variables and Diabetes Control Parameters

Demographic variables included age, sex, education completed (less than high school, high school, some college, college, graduate school), ethnic and racial group by self-report (American Indian/Alaska Native, Asian, Hawaiian/Pacific Islander, Black, Hispanic, White), and yearly income level. Measures of diabetes management were chosen per usual clinical practice and included HbA_{1c}, LDL, and systolic BP (SBP) and diastolic BP (DBP) at the baseline examination. We categorized diabetes control parameters according to existing recommendations. HbA_{1c} was categorized based on American Diabetes Association (ADA) standards-of-care thresholds (11,13) as <7% (53 mmol/mol), 7–7.9% (53–63 mmol/mol), and ≥8% (64 mmol/mol). LDL was categorized as <70 mg/dL, 70–99 mg/dL, and ≥100 mg/dL according to ADA standards of care (14). SBP was categorized according to thresholds tested in ACCORD (15) and the Systolic Blood Pressure Intervention Trial (SPRINT) (16) as <120 mmHg, 120–139 mmHg, and ≥140 mmHg. DBP was categorized as <80 mmHg, 80–89 mmHg, and ≥90 mmHg.

Covariates

Covariates and other variables of interest included history of depression, use of diabetes medications, duration of diabetes, use of hypertension medications, use of statins, and general health measured with the 36-Item Short Form Survey (SF-36) (17).

Statistical Analyses

We examined whether cognitive test scores had a normal distribution. None required transformation. The relation of categories of demographic variables and diabetes control parameters with

cognitive test scores was examined by comparing simple (unadjusted) means and means from ANCOVA adjusted for age, sex, and educational attainment. Adjustment for multiple comparisons was conducted using a Benjamini-Hochberg procedure, which controls the false discovery rate (i.e., the expected proportion of false-positive results among the significant tests observed). The tables show results for unadjusted (raw scores, model 1) and adjusted comparisons (scores adjusted for age, sex, education, and the general health question from the SF-36, model 2) and report unadjusted *P* values and *P* values adjusted for the false discovery rate. Results are reported as significant if the *P* value adjusted for the false discovery rate was <0.05. For significant results, we estimated Cohen's D as a standardized estimate of effect size (18). Cohen's D was calculated as the difference in adjusted means divided by the pooled SD and is usually interpreted as representing small (0.2), medium (0.5), or large effect sizes (0.8) (18), but these descriptions are arbitrary.

RESULTS

Table 1 shows the baseline characteristics of the sample. Among the 5,047 participants recruited into GRADE, 5,018 (99.4%) completed cognitive assessments. Participants' 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 HbA_{1c} measured at baseline was 7.5 ± 0.5% (58 ± 3.1 mmol/mol).

Demographic Variables and Cognitive Performance

We examined the relation of cognitive test scores with demographic variables, and results were as expected. Performance in all cognitive tests was lower with increasing age (Supplementary Table 1). Women performed better than men in all tests except animal fluency (Supplementary Table 2). Cognitive performance in all tests was higher with higher educational achievement (Supplementary Table 3).

Table 1—Baseline characteristics of study participants in GRADE

Characteristic	Value
Sample size, *n*	5,047
Female sex	1,837 (36.4)
Age, years	56.7 ± 10.0
Age-groups, years	
<50	1,209 (24.0)
50–64	2,628 (52.1)
≥65	1,210 (24.0)
Racial and ethnic group	
American Indian/Alaska Native	137 (2.7)
Asian	182 (3.6)
Hawaiian/Pacific Islander	28 (0.6)
Black or African American	1,000 (19.8)
White	3,314 (65.7)
Other/multiple	319 (6.3)
Unknown/not reported	67 (1.3)
Hispanic	929 (18.6)
Duration of diabetes, years	4.0 ± 2.7
HbA_{1c} at baseline	
%	7.5 ± 0.5
mmol/mol	58 ± 5.5
Groups	
6.8% to <7%	725 (14.4)
7% to <8%	3,276 (64.9)
8% to 8.5%	1,046 (20.7)
Highest level of school achieved	
Less than high school	364 (7.2)
High school/GED	1,039 (20.6)
Some college	1,463 (29.0)
College	1,332 (26.4)
Graduate school	848 (16.8)
Weight, kg	100.0 ± 22.3
BMI, kg/m^2	34.3 ± 6.8
Waist circumference, cm	112.3 ± 15.8
SBP, mmHg	128.3 ± 14.7
SBP groups, mmHg	
<120	1,449 (28.7)
120 to <140	2,514 (49.8)
≥140	1,082 (21.4)
DBP, mmHg	77.3 ± 9.9
DBP groups, mmHg	
<80	3,043 (60.3)
80 to <90	1,506 (29.9)
≥90	496 (9.8)
History of hypertension	3,670 (72.7)
LDL, mg/dL	90.5 ± 31.7
LDL groups, mg/dL	
<70	1,320 (27.2)
70 to <100	1,831 (37.7)
≥100	1,700 (35.0)
Statin use	3,209 (63.6)
Depression or depression medications	672 (13.3)
General health (single question)	
Very good or excellent	1,583 (31.4)
Good	2,519 (50.0)
Fair or poor	941 (18.7)

Data are *n* (%) or mean ± SD unless otherwise indicated. GED, general educational development.

Diabetes Control Parameters and Cognitive Performance

Baseline HbA_{1c} was not related to any of the cognitive tests after adjustment for multiple comparisons (Table 2). Higher LDL was related to lower scores in the DSST but was not related to performance in the SEVLT or letter fluency tests (Table 3). Cohen's D for the difference in adjusted DSST score between an LDL >100 and <70 mg/dL was 0.1 (a very small difference). SBP was not related to SEVLT or letter fluency performance (Table 4), but it had a nonlinear association with the DSST and animal fluency test such that participants with SBP between 120 and 139 mmHg had better performance than those with SBP <120 or >140 mmHg, although the difference size was very small. Cohen's D for the difference between SBP <120 and SBP 120 to ≤140 mmHg was 0.08, while it was 0.06 for the difference between SBP >140 mmHg and SBP 120 to ≤140 mmHg. DBP was not associated with performance in the SELVT or fluency test (Table 2) but had a nonlinear association with DSST such that participants with DBP between 80 and 89 mmHg had better performance than those with DBP <80 or >90 mmHg. These differences were also very small. Cohen's D for the difference between DBP <80 and 80 to ≤90 mmHg was 0.06, while it was 0.14 for the difference between DBP >90 and 80 to ≤90. Given the unexpected finding of a nonlinear association of DBP and SBP with DSST performance, we conducted post hoc analyses with the addition of hypertension treatment as a covariate, and the results remained unchanged.

We also examined the association of a history of hypertension with cognitive performance (Supplementary Table 4). Individuals with a history of hypertension compared with those without hypertension had lower performance in the DSST in an unadjusted analysis (DSST score 45.5 ± 13.6 vs. 47.4 ± 14.2; $P < 0.001$) that became nonsignificant after adjustment for age, sex, education, and general health (DSST score 42.1 ± 31.2 vs. 42.2 ± 25.7; $P = 0.965$). There were no other differences in cognitive scores between participants with and without hypertension.

Finally, we examined the relation of statin use with cognitive performance (Supplementary Table 5). Statin use versus no statin use was related to higher performance in DSST after adjustment for age, sex, education, and general health (DSST score 42.7 ± 26.2 vs. 41.3 ± 29.0), which was significant after adjustment for multiple tests ($P < 0.001$), although the size difference was small. Cohen's D for this difference was 0.1.

In post hoc linear regression analyses, we examined whether diabetes duration was associated with cognitive performance by adjusting for demographics. We found that diabetes duration was not related to performance in the SEVLT immediate recall (coefficient = 0.01; $P = 0.77$) or delayed recall (coefficient = 0.00; $P = 0.94$), animal fluency (coefficient = 0.01; $P = 0.51$), and DSST (coefficient = −0.03; $P = 0.53$) but was associated with a higher score in letter fluency (coefficient = 0.06; $P = 0.0061$). However, this significant post hoc result did not remain significant when adjusted for multiple comparisons.

CONCLUSIONS

We found that two of the three diabetes control parameters (glycemia, lipids, BP) that are generally used in clinical practice for type 2 diabetes management were modestly related to executive cognitive function. While glycemic control was not related to cognitive test performance, higher LDL was related to modestly lower executive function, and use of statins was related to modestly better executive function. SBP control between 120 and 139 mmHg, but not <120 mmHg,

Table 2—ANCOVA comparing scores of cognitive tests among HbA_{1c} groups

Cognitive test	HbA_{1c} <7% (53 mmol/mol)	HbA_{1c} 7–7.9% (53–63 mmol/mol)	HbA_{1c} ≥8% (8 mmol/mol)	*P* value Unadjusted	*P* value Adjusted
Participants, *n*	725	3,276	1,046		
SEVLT-I					
Model 1	25.3 ± 6.1	25.2 ± 5.9	25.5 ± 5.8	0.270	0.378
Model 2	24.6 ± 16.9	24.4 ± 11.6	24.7 ± 15.0	0.278	0.389
SEVLT-D					
Model 1	9.3 ± 2.7	9.3 ± 2.7	9.5 ± 2.6	0.014	0.033
Model 2	9.2 ± 7.8	9.1 ± 5.3	9.3 ± 6.9	0.027	0.061
Letter fluency					
Model 1	12.1 ± 4.3	12.4 ± 4.5	12.5 ± 4.3	0.151	0.240
Model 2	11.50 ± 13.58	11.83 ± 9.26	11.89 ± 12.0	0.122	0.201
Animal fluency					
Model 1	18.9 ± 5.3	19.2 ± 5.3	19.5 ± 5.6	0.055	0.108
Model 2	17.7 ± 16.3	18.1 ± 11.1	18.4 ± 14.5	0.044	0.091
DSST					
Model 1	45.5 ± 13.8	45.8 ± 13.5	46.9 ± 14.6	0.050	0.102
Model 2	41.9 ± 37.8	42.0 ± 25.8	42.8 ± 33.6	0.159	0.249

Data are mean ± SD unless otherwise indicated. Higher scores on these tests represent better performance. Model 1 is unadjusted. Model 2 is adjusted for age, sex, education, and the general health question from the SF-36. Shown are *P* values unadjusted for multiple comparisons and *P* values adjusted for multiple comparisons using the Benjamini-Hochberg procedure, which controls the false discovery rate. SEVLT-D, Spanish English Verbal Learning Test delayed recall; SEVLT-I, Spanish English Verbal Learning Test immediate recall.

Table 3—ANCOVA comparing scores of cognitive tests among LDL groups

Cognitive test	LDL, mg/dL			*P* value	
	<70	70 to <100	≥100	Unadjusted	Adjusted
Participants, *n*	1,320	1,831	1,700		
SEVLT-I					
Model 1	24.8 ± 5.8	25.4 ± 5.9	25.4 ± 5.9	0.006	0.015
Model 2	24.5 ± 14.4	24.6 ± 13.1	24.2 ± 13.0	0.150	0.240
SEVLT-D					
Model 1	9.2 ± 2.7	9.4 ± 2.6	9.4 ± 2.7	0.028	0.064
Model 2	9.2 ± 6.6	9.2 ± 6.0	9.0 ± 6.0	0.113	0.194
Letter fluency					
Model 1	12.3 ± 4.3	12.4 ± 4.4	12.5 ± 4.6	0.318	0.431
Model 2	11.68 ± 11.5	11.66 ± 10.4	11.85 ± 10.3	0.384	0.493
Animal fluency					
Model 1	19.3 ± 5.4	19.2 ± 5.3	19.0 ± 5.5	0.333	0.448
Model 2	18.1 ± 13.9	18.1 ± 12.6	17.9 ± 12.5	0.429	0.526
DSST					
Model 1	45.7 ± 13.5	46.6 ± 13.7	45.6 ± 14.2	0.063	0.121
Model 2	42.9 ± 32.1	42.6 ± 29.1	41.1 ± 28.8	<0.001	<0.001

Data are mean ± SD unless otherwise indicated. Higher scores on these tests represent better performance. Model 1 is unadjusted. Model 2 is adjusted for age, sex, education, and the general health question from the SF-36. Shown are *P* values unadjusted for multiple comparisons and *P* values adjusted for multiple comparisons using the Benjamini-Hochberg procedure, which controls the false discovery rate. SEVLT-D, Spanish English Verbal Learning Test delayed recall; SEVLT-I, Spanish English Verbal Learning Test immediate recall.

was related to modestly higher performance in executive function. Similarly, DBP control between 80 and 89 mmHg, but not <80 mmHg, was related to modestly higher executive function. A history of hypertension was not related to cognitive function. The reported associations between demographic variables and cognitive function were all in the expected direction, providing internal validation of our cognitive measures.

Contrary to our hypothesis, we did not find an association between glycemic control and performance in cognitive tests. The DCCT reported that worse glycemic control was related to lower performance in tests of executive function (2). In ACCORD, higher glycemia was related to lower performance in all cognitive tests at baseline (19), including tests of executive function and memory, with the strongest association for the DSST, the only test for which we found

Table 4—ANCOVA comparing scores of cognitive tests among groups of SBP and DBP

Cognitive test	SBP, mmHg			*P* value		DBP, mmHg			*P* value	
	<120	120 to <140	≥140	Unadjusted	Adjusted	<80	80 to <90	≥90	Unadjusted	Adjusted
Participants, *n*	1,449	2,514	1,082			3,043	1,506	496		
SEVLT-I										
Model 1	25.3 ± 5.8	25.4 ± 5.9	24.9 ± 5.9	0.057	0.111	25.1 ± 5.9	25.4 ± 5.8	25.6 ± 6.1	0.089	0.161
Model 2	24.3 ± 13.5	24.6 ± 12.3	24.5 ± 15.0	0.191	0.293	24.5 ± 11.6	24.5 ± 13.8	24.5 ± 19.6	0.977	0.988
SEVLT-D										
Model 1	9.4 ± 2.7	9.3 ± 2.7	9.2 ± 2.7	0.089	0.161	9.3 ± 2.7	9.4 ± 2.7	9.6 ± 2.5	0.041	0.087
Model 2	9.1 ± 6.2	9.1 ± 5.6	9.2 ± 6.9	0.969	0.986	9.2 ± 5.3	9.1 ± 6.3	9.2 ± 9.0	0.956	0.984
Letter fluency										
Model 1	12.3 ± 4.5	12.5 ± 4.5	12.3 ± 4.3	0.135	0.218	12.4 ± 4.5	12.4 ± 4.3	12.6 ± 4.4	0.491	0.586
Model 2	11.68 ± 10.8	11.91 ± 9.81	11.74 ± 12.0	0.215	0.316	11.84 ± 9.2	11.70 ± 11.0	11.81 ± 15.7	0.578	0.670
Animal fluency										
Model 1	19.0 ± 5.3	19.5 ± 5.5	18.8 ± 5.3	<0.001	<0.001	19.2 ± 5.4	19.3 ± 5.3	19.3 ± 5.4	0.687	0.767
Model 2	17.9 ± 12.9	18.4 ± 11.8	17.8 ± 14.4	0.001	0.003	18.2 ± 11.1	18.0 ± 13.3	17.8 ± 18.9	0.194	0.296
DSST										
Model 1	45.8 ± 14.0	46.7 ± 13.6	44.8 ± 14.0	<0.001	0.002	45.2 ± 13.5	47.5 ± 14.0	46.6 ± 14.5	<0.001	<0.001
Model 2	41.6 ± 30.1	42.7 ± 27.3	41.8 ± 33.5	0.014	0.032	42.0 ± 25.8	42.8 ± 30.8	40.9 ± 43.8	0.004	0.010

Data are mean ± SD unless otherwise indicated. Higher scores on these tests represent better performance. Model 1 is unadjusted. Model 2 is adjusted for age, sex, education, and the general health question from the SF-36. Shown are *P* values unadjusted for multiple comparisons and *P* values adjusted for multiple comparisons using the Benjamini-Hochberg procedure, which controls the false discovery rate. SEVLT-D, Spanish English Verbal Learning Test delayed recall; SEVLT-I, Spanish English Verbal Learning Test immediate recall.

significant associations in GRADE. DCCT participants (average age 46 years) had a mean diabetes duration of 24 years, and ACCORD participants (average age 62 years) had a mean duration of diabetes of >10 years. The mean duration of diabetes among GRADE participants at entry was ~4 years, much shorter than in ACCORD or DCCT, and the age was older than in DCCT and similar to ACCORD. Given these comparisons, it seems reasonable to speculate that in people with diabetes duration of <10 years, the association between glycemia and cognitive performance may not yet be evident.

Our finding that higher LDL is related to modestly lower executive function was not surprising since LDL >100 mg/dL is a risk factor for cerebrovascular disease (20), and a lower DSST score is a good proxy for the executive cognitive impairment caused by cerebrovascular injury (18,21). Congruent with this finding, we found that statin use was related to modestly better executive function. The U.S. Food and Drug Administration has issued a warning on the potential adverse effects of statins on cognition, despite a lack of evidence in clinical trials of such adverse effects (22). Our analyses were cross sectional, limiting the inferences that can be made about these results. Nonetheless, these results suggest to patients with type 2 diabetes and their care providers that aiming for lower LDL with statins as currently recommended in people with diabetes (14) appears to be safe for cognition, but long-term follow-up is warranted.

Our results for SBP and DBP are complex and merit further discussion, although the reported differences are modest and may not be clinically significant. Although our study is cross sectional, the association of SBP and DBP and executive function suggests that SBP and DBP control <120 and 80 mmHg, respectively, is not associated with better executive function, but control as currently recommended (12,14) of SBP of 120–139 and DBP of 80–89 mmHg is related to better executive function compared with higher levels. Recent results of the SPRINT trial in a sample without type 2 diabetes support the notion that targeting SBP to <120 mmHg is beneficial for cognitive impairment (23) and cerebrovascular disease (24). However, ACCORD did not find a benefit for intensive hypertension control for cardiovascular events (15) or cognition (25) among people with diabetes, suggesting that the benefit of tight hypertension control (SBP <120 mmHg) may not apply to those with type 2 diabetes. Our finding of a nonlinear association between BP levels and performance in the DSST was independent of hypertension treatment, and other potential explanations need to be considered. Since our study is cross sectional, it is not possible to know whether people who are more likely to have lower cognitive performance have brain pathology accompanied by brain BP dysregulation (26) leading to lower SBP and lower DBP, which could explain our results. However, adjustment for confounders did not change the relationship. We can speculate that tight hypertension control in people with diabetes may lead to brain hypoperfusion and worse cognitive performance, but this hypothesis cannot be directly addressed by our study. A history of hypertension was not related to worse cognitive performance among GRADE participants, suggesting that among people with a relatively short duration of type 2 diabetes, history of hypertension has not yet impacted cognitive performance.

Our study has notable strengths and limitations. Strengths include the large sample size, standardized central training of research staff conducting assessments, and the robust relationship of demographic variables with cognitive variables in the expected direction, providing confidence that we have the statistical power and sensitive cognitive measures to evaluate modifiers of cognitive performance. The main limitation of our study is its cross-sectional nature, which limits the inferences that can be made about causality. It is possible that our null finding for HbA_{1c} could be explained by the relatively narrow range in the inclusion criteria (6.8–8.5% [51–69 mmol/mol]), and we cannot address whether HbA_{1c} values above this range are related to cognitive performance. Sleep apnea is more common in obese people with diabetes (27) and is related to worse cognitive performance (28), but we did not have data on sleep apnea and could not account for this important covariate. GRADE did not conduct a formal cognitive screen at study entry. However, it seems unlikely that the cohort included people with significant cognitive impairment given the relatively young age of the cohort. People with major cardiovascular events within 1 year of study entry were excluded. Thus, our findings may be generalizable only to people with type 2 diabetes of a few years' duration without significant cognitive impairment and cardiovascular disease. Another limitation is that women represented only 36% of the sample, which further limits generalizability. Finally, the effect estimates for the associations we report were very small, smaller than reported in existing literature on cognition in type 2 diabetes (1), and the clinical significance of our findings is uncertain. A potential explanation for the small differences compared with those previously reported is that the GRADE cohort is relatively young with a healthier cardiovascular profile and shorter diabetes duration compared with other studies. We cannot address whether the differences observed in cognitive performance affect compliance with diabetes treatment, quality of life, or overall function. Analyses of longitudinal data once the trial is completed may allow us to address the clinical significance of findings for cognitive function and to make inferences about causality.

In conclusion, in people with type 2 diabetes of <5 years' duration on average, lower LDL levels, use of statins, SBP control in the 120–139-mmHg range, and DBP control in the 80–90-mmHg range, are related to modestly better executive cognitive performance. These modest differences may not be clinically significant given the very small size of the differences. However, our findings for statins are reassuring given the reported concerns for adverse effects of statins on cognitive function. Longitudinal follow-up will allow us to evaluate whether the observed differences increase in size, revert, or are stable.

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References

1. Biessels GJ, Strachan MWJ, Visseren FLJ, Kappelle LJ, Whitmer RA. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. Lancet Diabetes Endocrinol 2014;2:246–255

2. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med 2007;356:1842–1852

3. Launer LJ, Miller ME, Williamson JD, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol 2011;10:969–977

4. Nathan DM, Buse JB, Kahn SE, et al.; GRADE Study Research Group. Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE). Diabetes Care 2013;36:2254–2261

5. Wexler DJ, Krause-Steinrauf H, Crandall JP, et al. Baseline characteristics of randomized participants in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes Care 2019;42:2098–2107

6. McDonagh J. Statin-related cognitive impairment in the real world: you'll live longer, but you might not like it. JAMA Intern Med 2014;174:1889

7. Small SA, Mayeux R. A clinical approach to memory decline. J Pract Psychiatry Behav Health 1999;5:87–94

8. Royall DR, Lauterbach EC, Cummings JL, et al. Executive control function: a review of its promise and challenges for clinical research. A report from the Committee on Research of the American Neuropsychiatric Association. J Neuropsychiatry Clin Neurosci 2002;14:377–405

9. González HM, Mungas D, Reed BR, Marshall S, Haan MN. A new verbal learning and memory test for English- and Spanish-speaking older people. J Int Neuropsychol Soc 2001;7:544–555

10. Wechsler D. *Wechsler Adult Intelligence Scale-Revised.* New York, Psychological Corporation, 1988

11. Goodglass H, Kaplan E. *Assessment of aphasia and related disorders.* Philadelphia, Lea and Febiger, 1983

12. Benton AL. *Multilingual Aphasia Examination.* Iowa City, University of Iowa, 1983

13. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes–2019*. Diabetes Care 2019;42(Suppl. 1):S61–S70

14. American Diabetes Association. 10. Cardiovascular disease and risk management: *Standards of Medical Care in Diabetes–2019*. Diabetes Care 2019;42(Suppl. 1):S103–S123

15. Buysse DJ, Yu L, Moul DE, et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. Sleep 2010;33:781–792

16. Wright JT Jr, Williamson JD, Whelton PK, et al.; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–2116

17. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–483

18. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. New York, Academic Press, 1988

19. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al.; Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) Investigators. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial. Diabetes Care 2009;32:221–226

20. Kernan WN, Ovbiagele B, Black HR, et al.; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160–2236

21. Hachinski V, Iadecola C, Petersen RC, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards [published correction appears in Stroke 2007;38:1118]. Stroke 2006;37:2220–2241

22. Ott BR, Daiello LA, Dahabreh IJ, et al. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. J Gen Intern Med 2015;30:348–358

23. SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. JAMA 2019;321:553–561

24. SPRINT MIND Investigators for the SPRINT Research Group. Association of intensive vs standard blood pressure control with cerebral white matter. JAMA 2019;322:524–534

25. Williamson JD, Launer LJ, Bryan RN, et al.; Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Investigators. Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. JAMA Intern Med 2014;174:324–333

26. Iadecola C, Gottesman RF. Neurovascular and cognitive dysfunction in hypertension. Circ Res 2019;124:1025–1044

27. Kuna ST, Reboussin DM, Strotmeyer ES, et al. Effects of weight loss on obstructive sleep apnea severity. Ten-year results of the Sleep AHEAD Study. Am J Respir Crit Care Med 2021;203:221–229

28. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 2011;306:613–619