# The Role of Hyperglycemia, Insulin Resistance, and Blood Pressure in Diabetes-Associated Differences in Cognitive Performance—The Maastricht Study

*Diabetes Care 2017;40:1537–1547 | https://doi.org/10.2337/dc17-0330*

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## OBJECTIVE

**To study to what extent differences in cognitive performance between individuals with different glucose metabolism status are potentially attributable to hyperglycemia, insulin resistance, and blood pressure–related variables.**

## RESEARCH DESIGN AND METHODS

**We used cross-sectional data from 2,531 participants from the Maastricht Study (mean age ± SD, 60 ± 8 years; 52% men; *n* = 666 with type 2 diabetes), all of whom completed a neuropsychological test battery. Hyperglycemia was assessed by a composite index of fasting glucose, postload glucose, glycated hemoglobin ($HbA_{1c}$), and tissue advanced glycation end products; insulin resistance by the HOMA of insulin resistance index; and blood pressure–related variables included 24-h ambulatory pressures, their weighted SDs, and the use of antihypertensive medication. Linear regression analyses were used to estimate mediating effects.**

## RESULTS

**After adjustment for age, sex, and education, individuals with type 2 diabetes, compared with those with normal glucose metabolism, performed worse in all cognitive domains (mean differences in composite *z* scores for memory −0.087, processing speed −0.196, executive function and attention −0.182; *P* values <0.032), whereas individuals with prediabetes did not. Diabetes-associated differences in processing speed and executive function and attention were largely explained by hyperglycemia (mediating effect 79.6% [bootstrapped 95% CI 36.6; 123.4] and 50.3% [0.6; 101.2], respectively) and, for processing speed, to a lesser extent by blood pressure–related variables (17.7% [5.6; 30.1]), but not by insulin resistance. None of the factors explained the differences in memory function.**

## CONCLUSIONS

**Our cross-sectional data suggest that early glycemic and blood pressure control, perhaps even in the prediabetic stage, may be promising therapeutic targets for the prevention of diabetes-associated decrements in cognitive performance.**


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*Received 13 February 2017 and accepted 23 July 2017.*

*This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-0330/-/DC1.*

*This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.*

Almost a century ago, Miles and Root (1) were the first to report a link between diabetes and cognitive performance. Since then, it has become evident that type 2 diabetes, the most common form of diabetes, as well as its precursor, prediabetes, are associated with a variety of cognitive changes, ranging from subtle cognitive decrements to frank dementia (2). The prevalence of these diabetes-associated cognitive problems is expected to rise dramatically as a result of the ongoing diabetes epidemic and the increasing life expectancy of individuals with diabetes (3), which highlights the need for preventive strategies. The exact mechanisms underlying diabetes-associated cognitive problems remain, however, incompletely understood, although metabolic and vascular factors are often considered to be involved (2,4,5).

Previous epidemiological studies (6–9) have focused mainly on whether the effects of type 2 diabetes on cognitive performance are independent of cardiovascular risk factors, which was partially the case, and have confirmed that markers of hyperglycemia, insulin resistance (IR), and vascular factors, particularly abnormalities in blood pressure, are associated with cognitive performance, irrespective of glucose metabolism status (10–12). It is unclear, however, to what extent these metabolic and vascular factors also mediate, and thus explain, diabetes-associated cognitive decrements. Therefore, the current study aimed to examine to what extent differences in cognitive performance between individuals with different glucose metabolism status (i.e., normal glucose metabolism [NGM], impaired glucose metabolism [prediabetes], and type 2 diabetes) are attributable to hyperglycemia, IR, and blood pressure–related variables.

## RESEARCH DESIGN AND METHODS

### Study Population

The present analysis was conducted with data from the Maastricht Study, an ongoing observational, prospective, population-based cohort study that focuses on the etiology, complications, and comorbidities of type 2 diabetes and is characterized by an extensive phenotyping approach. Individuals eligible to participate are those between the ages of 40 and 75 years who live in the southern part of the Netherlands and are sufficiently proficient in the Dutch language. The Maastricht Study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sport of the Netherlands, on the basis of the opinion of the Health Council (Permit 131088-105234-PG).

For the current study, cross-sectional data from the first 3,451 participants who completed the baseline survey between November 2010 and September 2013 were used. We excluded participants with types of diabetes other than type 2 ($n$ = 41 [of whom 37 had type 1 diabetes]).

### Glucose Metabolism Status

A 2-h seven-sample oral glucose tolerance test (OGTT) was used to determine the participants' glucose metabolism status. According to the 2006 World Health Organization diagnostic criteria (13), glucose metabolism status was classified as NGM, prediabetes, or diabetes. Participants receiving glucose-lowering medication without a prior diagnosis of type 1 diabetes were considered to have type 2 diabetes, regardless of the OGTT results. For safety reasons, participants receiving insulin and those with a fasting glucose level >11.0 mmol/L were excluded from the OGTT (14).

### Cognitive Performance

Participants of the Maastricht Study are subjected to a concise (30 min) neuropsychological test battery (14) that follows recommendations (15) for the assessment of diabetes-associated cognitive problems. It therefore includes tests that are able to detect subtle differences in cognitive performance. For the current study, to enhance conceptual clarity, raw test scores were standardized and divided into three cognitive domains (i.e., memory function, executive function and attention [EF&A], and information processing speed). As detailed previously (16), the composite $z$ score for memory was derived from the verbal learning test by averaging total immediate and delayed recall scores. The composite $z$ score for information-processing speed was derived from the Stroop Color Word Test Parts I and II, the Concept Shifting Test Parts A and B, and the Letter-Digit Substitution Test. EF&A was assessed by the Stroop Color Word Test Part III and the Concept Shifting Test Part C. Where necessary, raw test scores were inverted so that higher scores indicated better cognitive performance.

### Hyperglycemia

In order to capture the exposure to hyperglycemia as completely and accurately as possible, we constructed a composite index of hyperglycemia that included fasting and postload plasma glucose levels as measures of short-term hyperglycemia, and glycated hemoglobin ($HbA_{1c}$) and tissue advanced glycation end product accumulation (based on skin autofluorescence [SAF]) as representatives of long-term hyperglycemia. To this end, individual measures were standardized into $z$ scores and averaged. Note that individuals receiving insulin had no data on postload glucose because they were excluded from the OGTT and, therefore, their composite index of hyperglycemia consisted of fasting glucose, $HbA_{1c}$, and SAF. For sensitivity analyses, we also constructed a composite index that focused on long-term hyperglycemia because fasting and postload glucose levels were directly used for the classification of glucose metabolism status.

Venous fasting and postload plasma glucose levels were measured by the enzymatic hexokinase method using automatic analyzers (Beckman Synchron LX20; Beckman Coulter Inc., Brea, CA; and Cobas 6000; Roche Diagnostics, Mannheim, Germany) (16). $HbA_{1c}$ was determined by ion-exchange high-performance liquid chromatography. SAF was measured with the AGE reader (DiagnOptics Technologies B.V., Groningen, the Netherlands) (17).

### IR

The HOMA-IR, calculated from fasting insulin and glucose levels, was used as an index of IR. HOMA-IR is the most widely used and validated surrogate marker of IR and corresponds reasonably well to clamp-derived measures of insulin sensitivity (18). There is, however, a great variety of surrogate markers available with no consensus on which marker to use (19). Therefore, in sensitivity analyses, IR was based on single fasting insulin measurements, HOMA-IR calculated with fasting C-peptide levels rather than insulin levels, the insulin sensitivity index (ISI) (20), and a composite index that combined the HOMA-IR and the ISI. Theoretically, and demonstrated experimentally (21), the HOMA-IR calculated with C-peptide might be a more stable marker of peripheral IR because C-peptide is not cleared by the liver. Likewise, the ISI

incorporated the response of the body to an oral glucose load but could not be calculated for individuals receiving insulin therapy because these were excluded from the OGTT.

Fasting and post–glucose load levels of insulin and C-peptide were quantified on a Meso Scale custom duplex assay (Meso Scale Discovery, Gaithersburg, MD) (16). The HOMA-calculator version 2.2.3 for Windows (https://www.dtu.ox.ac.uk/homacalculator) was used to calculate the HOMA indices. The ISI was calculated as suggested by DeFronzo and Matsuda (20), whereby the reciprocal (i.e., 1/ISI) was used to reflect IR.

### Blood Pressure–Related Variables

Based on 24-h ambulatory blood pressure data, a composite index was created that incorporated systolic and diastolic blood pressure and their weighted SDs. Blood pressure variability was included because it is increasingly recognized to be associated with worse cognitive performance (22) and an increased dementia risk (23), independent of actual blood pressure. For the analyses, this composite index was combined with the use of antihypertensive medication in order to account for previous exposure to elevated blood pressure levels. The use of antihypertensive medication could not be directly incorporated in the composite index because it is a dichotomous variable. For sensitivity analyses, we also constructed an index that included 24-h pulse pressure rather than 24-h systolic and diastolic blood pressure because arterial stiffening has been linked to cognitive performance (24).

In order to obtain data on blood pressure, participants were requested to undergo 24-h blood pressure monitoring (WatchBP03; Microlife AG, Widnau, Switzerland) (14,25). Average 24-h systolic and diastolic blood pressure, as well as short-term blood pressure variability, were determined following the recommendations of the British Hypertension Society as detailed previously (25). The use of antihypertensive medication was ascertained by a medication interview (14).

### Covariates

Educational level, classified as low/intermediate/high, was ascertained by interview (14). Details on the assessment of cardiovascular risk factors (i.e., waist circumference, total/HDL cholesterol ratio, and smoking behavior) can be found in previous reports (14,16,25). Prior cardiovascular disease was defined as a history of myocardial infarction, stroke, or arterial surgery (14). Microvascular disease was defined as the presence of albuminuria and/or retinopathy. The presence of albuminuria was based on urinary albumin excretion in preferably two 24-h urine collections (26). Fundus photography of both eyes was performed using an auto fundus camera (AFC-230; Nidek, Gamagori, Japan) to assess the presence of retinopathy. The presence of depressive symptoms was evaluated with the use of the Mini International Neuropsychiatric Interview (27). The occurrence of hypoglycemic events over the preceding year was ascertained by questionnaire (14).

### Statistical Analyses

The age-, sex-, and education-adjusted associations of glucose metabolism status with cognitive performance were estimated by linear regression analyses with cognitive performance as the dependent variable. Individuals with NGM served as the reference group. Linear regression analyses were also used to analyze the associations between, on the one hand, the indices used for hyperglycemia, IR, and blood pressure, and, on the other hand, cognitive performance. Next, using multiplicative interaction terms, we examined whether these associations differed by glucose metabolism status, with age, sex, and educational level as covariates. We also tested for pairwise statistical interaction among the indices used for hyperglycemia, IR, and blood pressure (e.g., hyperglycemia $\times$ IR) with regard to their association with cognitive performance.

The extent to which hyperglycemia, IR, and blood pressure–related variables mediated the association between glucose metabolism status and cognitive performance was then determined by adding these variables to the initially described regression models. Both independent and joint mediation effects were evaluated and expressed as the (percentage) change of the regression coefficients of the dummies coding glucose metabolism status. Corresponding 95% CI were estimated with the use of an SPSS macro provided by Preacher and Hayes (28) (10,000 bootstrap iterations). Note that these bootstrapped CIs were created around the change in regression coefficients and do not account for the uncertainty of the actual regression coefficients reflecting the prediabetes- and diabetes-associated differences in cognitive performance. Consequently, the estimated mediating effect may be $<0$ or $>100\%$, especially when there is correlation between the independent and potential mediator factor, which decreases the statistical power of the mediation analyses (29), thereby widening the CIs. We also analyzed the mediating effects of the individual components of the composite indices. Collinearity diagnostics (i.e., tolerance $<0.1$ and/or variance inflation factor $>10$) were used to detect multicollinearity between the independent variables.

Multiple sensitivity analyses were performed to test the robustness of our findings and that of the composite indices we constructed. First, we evaluated whether the extent of mediation differed between individuals with newly diagnosed type 2 diabetes and those with a known diagnosis of diabetes at study entry. Second, we explored the effects of additional adjustment for cardiovascular risk factors (i.e., waist circumference, total/HDL cholesterol ratio, smoking behavior, and history of cardiovascular disease) and the presence of depression, as well as the mediating effects that these variables themselves had. In a separate analysis, we also evaluated the mediating effects of microvascular disease, which could serve as a pathway through which hyperglycemia and blood pressure abnormalities may affect cognitive performance. Third, to investigate whether the results depended on how the composite indices were constructed, the mediating effects of hyperglycemia were reexplored with a focus on long-term hyperglycemia, those of IR were reassessed with IR being defined in multiple alternative ways, and those of blood pressure–related variables were reanalyzed without considering the use of antihypertensive medication and with a composite index that included 24-h pulse pressure rather than systolic and diastolic blood pressure. Finally, we explored the mediating effects of hypoglycemia and reanalyzed the data excluding participants on insulin therapy because the HOMA-IR index has not been validated adequately for individuals receiving

**Table 1—Characteristics of the study population**

| | Total (*n* = 2,531) | NGM (*n* = 1,479) | Prediabetes (*n* = 386) | T2DM (*n* = 666) | *P* value for trend* |
|---|---|---|---|---|---|
| Age (years) | 60 ± 8 | 58 ± 8 | 62 ± 7 | 63 ± 8 | <0.001 |
| Male sex | 1,314 (52.0) | 651 (44.0) | 207 (53.6) | 456 (68.5) | <0.001 |
| Educational level | | | | | <0.001 |
| Low | 388 (15.3) | 151 (10.2) | 70 (18.1) | 167 (25.1) | <0.001 |
| Middle | 1,110 (43.9) | 643 (43.5) | 165 (42.7) | 302 (45.3) | <0.001 |
| High | 1,033 (40.8) | 685 (46.3) | 151 (39.1) | 197 (29.6) | <0.001 |
| Fasting glucose (mmol/L) | 5.5 [5.1–6.4] | 5.2 [4.9–5.5] | 6.1 [5.5–6.3] | 7.4 [6.7–8.4] | <0.001 |
| 2 h after OGTT glucose (mmol/L)† | 6.2 [5.1–9.1] | 5.4 [4.6–6.2] | 8.4 [7.2–9.4] | 14.4 [11.9–17.2] | <0.001 |
| $HbA_{1c}$ (%) | 5.9 ± 0.8 | 5.5 ± 0.3 | 5.7 ± 0.4 | 6.8 ± 1.0 | <0.001 |
| $HbA_{1c}$ (mmol/mol) | 41 ± 9 | 36 ± 4 | 39 ± 5 | 51 ± 11 | <0.001 |
| SAF (AU) | 2.44 ± 0.54 | 2.33 ± 0.50 | 2.47 ± 0.51 | 2.66 ± 0.58 | <0.001 |
| Diabetes duration (years) | | | | 6.0 [3.0–12.0]‡‡ | |
| Glucose-lowering medication, any type | | | | 512 (76.9) | |
| Insulin | | | | 143 (21.5) | |
| Oral glucose-lowering medication | | | | 480 (72.1) | |
| Fasting insulin (pmol/L) | 61 [42–92] | 53 [38–74] | 71 [45–100] | 84 [53–127] | <0.01 |
| Fasting C-peptide (pmol/L)‡ | 600 [454–824] | 538 [418–689] | 698 [515–889] | 789 [539–1,073] | <0.01 |
| HOMA-IR (AU) | 1.2 [0.8–1.8] | 1.0 [0.7–1.4] | 1.4 [0.9–2.2] | 1.7 [1.1–2.6] | <0.001 |
| 24-h SBP (mmHg) | 119 ± 12 | 117 ± 11 | 120 ± 11 | 122 ± 12 | <0.001 |
| 24-h DBP (mmHg) | 73 ± 7 | 73 ± 7 | 74 ± 7 | 73 ± 7 | 0.173 |
| Weighted 24-h SD of SBP (mmHg) | 11 [9–13] | 11 [9–13] | 11 [9–13] | 12 [10–14] | <0.001 |
| Weighted 24-h SD of DBP (mmHg) | 8 [7–10] | 8 [7–10] | 8 [7–10] | 9 [7–10] | <0.001 |
| Antihypertensive medication | 978 (38.6) | 338 (22.9) | 169 (43.8) | 471 (70.7) | <0.001 |
| Waist circumference (cm)§ | 95 ± 13 | 91 ± 11 | 98 ± 12 | 105 ± 13 | <0.001 |
| BMI ($kg/m^2$)‡ | 26.9 ± 4.3 | 25.6 ± 3.6 | 27.6 ± 4.1 | 29.4 ± 4.6 | <0.01 |
| Total cholesterol (mmol/L) | 5.3 ± 1.2 | 5.6 ± 1.0 | 5.5 ± 1.1 | 4.5 ± 1.0 | <0.001 |
| HDL cholesterol (mmol/L) | 1.5 ± 0.5 | 1.6 ± 0.5 | 1.5 ± 0.4 | 1.3 ± 0.4 | <0.001 |
| LDL cholesterol (mmol/L) | 3.1 ± 1.0 | 3.4 ± 0.9 | 3.3 ± 1.0 | 2.4 ± 0.9 | <0.001 |
| Total/HDL cholesterol ratio | 3.7 ± 1.2 | 3.6 ± 1.2 | 3.9 ± 1.1 | 3.7 ± 1.1 | 0.052 |
| Triglycerides (mmol/L) | 1.2 [0.9–1.7] | 1.1 [0.8–1.5] | 1.4 [1.0–1.8] | 1.5 [1.1–2.2] | <0.001 |
| Lipid-modifying medication | 879 (34.7) | 256 (17.3) | 130 (33.7) | 493 (74.0) | <0.001 |
| Smoking behavior¶ | | | | | <0.001 |
| Never | 870 (35.0) | 579 (39.6) | 111 (29.2) | 180 (27.9) | <0.001 |
| Former | 1,304 (52.4) | 715 (48.9) | 221 (58.2) | 368 (57.1) | <0.001 |
| Current | 313 (12.6) | 168 (11.5) | 48 (12.6) | 97 (15.0) | <0.001 |
| Prior cardiovascular diseases# | 399 (16.3) | 173 (12.0) | 46 (12.2) | 180 (28.3) | <0.001 |
| Current depression** | 136 (5.4) | 63 (4.3) | 16 (4.2) | 57 (8.6) | <0.001 |

*Continued on p. 1541*

**Table 1—Continued**

| | Total ($n$ = 2,531) | NGM ($n$ = 1,479) | Prediabetes ($n$ = 386) | T2DM ($n$ = 666) | $P$ value for trend* |
|---|---|---|---|---|---|
| Verbal learning test | | | | | |
| Total immediate recall (words) | 44 ± 10 | 46 ± 9 | 44 ± 10 | 41 ± 9 | <0.01 |
| Delayed recall (words) | 9 ± 3 | 10 ± 3 | 9 ± 3 | 8 ± 3 | <0.01 |
| Stroop Color Word Test†† | | | | | |
| Part I (s) | 44.5 [40.3–50.1] | 43.2 [39.4–48.5] | 44.6 [39.5–48.8] | 47.1 [42.2–53.0] | <0.01 |
| Part II (s) | 57.9 [51.9–65.6] | 56.4 [50.9–63.3] | 56.6 [51.8–62.5] | 61.5 [55.0–70.1] | <0.01 |
| Part III, adjusted for parts I and II (s) | 41.7 [32.5–54.1] | 39.1 [30.7–49.5] | 42.3 [35.5–53.2] | 48.2 [36.9–64.5] | <0.01 |
| Concept Shifting Test†† | | | | | |
| Part A (s) | 20.7 [17.4–24.4] | 20.0 [16.7–23.4] | 20.2 [17.8–24.1] | 22.3 [18.9–26.1] | <0.01 |
| Part B (s) | 24.3 [20.8–28.9] | 23.1 [20.0–27.5] | 24.3 [20.2–30.1] | 26.5 [22.6–31.4] | <0.01 |
| Part C, adjusted for parts A and B (s) | 8.8 [4.9–14.5] | 8.1 [4.6–13.0] | 9.7 [5.2–16.7] | 10.7 [6.0–16.8] | <0.01 |
| Letter-digit substitution test (no. of substitutions) | 49 ± 9 | 51 ± 9 | 48 ± 10 | 45 ± 9 | <0.01 |

Data are presented as the mean ± SD, median [interquartile range], or $n$ (%). AU, arbitrary units; DBP, diastolic blood pressure; SBP, systolic blood pressure; T2DM, type 2 diabetes. *$P$ value for trend as determined with use of one-way ANOVA for continuous variables and $\chi^2$ tests for categorical variables. †$n$ = 2,388. ‡$n$ = 2,529. §$n$ = 2,528. ¶$n$ = 2,487. #$n$ = 2,454. **$n$ = 2,513. ††For the Stroop Color Word Test and Concept Shifting Test, longer times indicate worse cognitive performance. ‡‡$n$ = 457.

insulin (18), although it has been suggested to be valid (30).

All analyses were conducted with SPSS version 22.0 for Windows (IBM, Armonk, NY) at a significance level of 5% except for the tests of interaction effects, where a significance level of 10% was used. No adjustments were made for multiple comparisons (31). Variables with a skewed distribution were transformed with the natural logarithm prior to analyses.

## RESULTS

### Study Population

From the 3,410 individuals who were initially eligible for the current study, 225 (6.6%) were excluded because they had no or incomplete data on cognitive performance, mostly because they were unwilling to undergo or were unmotivated to complete the cognitive assessment. An additional 654 individuals (19.2%) were excluded because of missing data on the composite indices of hyperglycemia ($n$ = 220 [of whom $n$ = 176 were missing data on SAF]), IR ($n$ = 46), and/or blood pressure abnormalities ($n$ = 437 [of whom $n$ = 365 had no data on 24-h blood pressure levels]), leaving 2,531 participants for the present analyses. Details on those who were excluded from the present analysis are provided in Supplementary Table 1. Demographic and clinical characteristics of the final study population, stratified by glucose metabolism status, are presented in Table 1. Of the 666 individuals who were classified as having type 2 diabetes, 103 (15.5%) were newly diagnosed at study entry.

### Glucose Metabolism Status and Cognitive Performance

Figure 1 shows the age-, sex-, and education-adjusted mean differences in cognitive performance between individuals with different glucose metabolism status. Despite an overall trend toward lower cognitive performance with deteriorating glucose metabolism status, statistically significant worse cognitive performance was observed only in individuals with diabetes. Detailed analyses revealed that these differences were primarily driven by the relatively poor cognitive performance of individuals with previously diagnosed diabetes. The magnitude of diabetes-associated worse cognitive performance was similar across cognitive

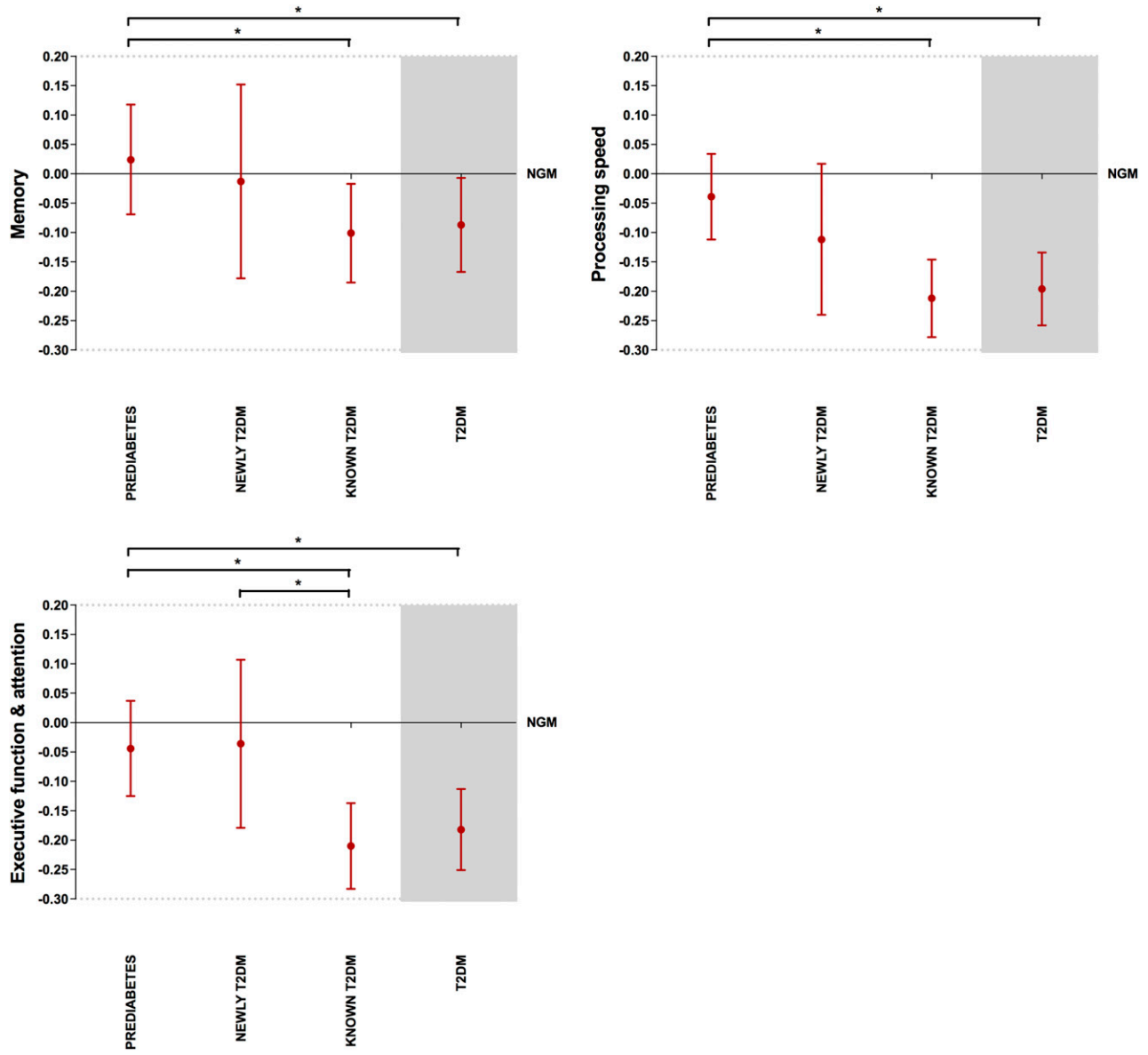


**Figure 1**—Association between glucose metabolism status and cognitive performance. Data are presented as unstandardized regression coefficients (95% CIs), which reflect the between-group differences in cognitive performance. Individuals with NGM were used as the reference group. All analyses were adjusted for age, sex, and educational level. *$P < 0.05$. KNOWN T2DM, previously diagnosed type 2 diabetes; NEWLY T2DM, newly diagnosed type 2 diabetes at study entry; T2DM, type 2 diabetes. For memory: T2DM vs. PREDIABETES $P = 0.035$; NEWLY T2DM vs. PREDIABETES $P = 0.678$; KNOWN T2DM vs. PREDIABETES $P = 0.022$; KNOWN T2DM vs. NEWLY T2DM $P = 0.319$. For processing speed: T2DM vs. PREDIABETES $P < 0.001$; NEWLY T2DM vs. PREDIABETES $P = 0.306$; KNOWN T2DM vs. PREDIABETES $P < 0.001$; KNOWN T2DM vs. NEWLY T2DM $P = 0.144$. For EF&A: T2DM vs. PREDIABETES $P = 0.003$; NEWLY T2DM vs. PREDIABETES $P = 0.917$; KNOWN T2DM vs. PREDIABETES $P < 0.001$; and KNOWN T2DM vs. NEWLY T2DM $P = 0.023$.

domains except for memory function, where the magnitude was less than half of that observed for processing speed and EF&A.

### Hyperglycemia, IR, Blood Pressure–Related Variables, and Cognitive Performance

After adjustment for age, sex, and educational levels, across the whole study population, statistically significant negative associations were found between the composite index of hyperglycemia and performance in the domains of processing speed and EF&A, between IR and performance in the domain of EF&A, and between the index of blood pressure–related variables and performance in all of the cognitive domains assessed (Table 2). Importantly, these associations did not differ statistically significantly by glucose metabolism status. We did, however, observe interaction between hyperglycemia and the use of antihypertensive medication in their association with performance in the domains of memory ($P$ for interaction = 0.009) and processing speed ($P$ for interaction = 0.035). Specifically, the presence of the one tended to exacerbate the negative effects of the other (Table 2). The direction of the associations with cognitive performance of the individual components of the composite indices was similar to that of the respective composite index (Table 3).

**Table 2—Associations between, on the one hand, the indices used for hyperglycemia, IR, and blood pressure–related variables and, on the other hand, cognitive performance**

| | Memory | Processing speed | EF&A |
|---|---|---|---|
| Hyperglycemia | −0.031 (0.105) | −0.132* (<0.001) | −0.103* (<0.001) |
| IR | −0.031 (0.079) | −0.032 (0.062) | −0.051* (0.005) |
| Blood pressure–related variables | | | |
| 24-h BP and their SD | 0.001 (0.967) | −0.018 (0.291) | −0.012 (0.515) |
| Use of antihypertensive medication | −0.085* (0.017) | −0.131* (<0.001) | −0.081* (0.009) |
| Individuals using antihypertensive medication | | | |
| Hyperglycemia | −0.068 (0.023) | −0.162 (<0.001) | −0.125 (<0.001) |
| Individuals not using antihypertensive medication | | | |
| Hyperglycemia | 0.027 (0.257) | −0.064 (0.006) | −0.059 (0.016) |
| Individuals with a hyperglycemia level above the mean | | | |
| Use of antihypertensive medication | −0.139 (0.015) | −0.171 (<0.001) | −0.053 (0.305) |
| Individuals with a hyperglycemia level below the mean | | | |
| Use of antihypertensive medication | −0.019 (0.696) | −0.045 (0.237) | −0.040 (0.342) |

*N* = 2,531. Data are presented as standardized regression coefficients (*P* values), except for the use of antihypertensive medication, where unstandardized regression coefficients (*P* values) are presented. All analyses are adjusted for age, sex, and educational level. Regression coefficients of 24-h BP and their SD are additionally adjusted for the use of antihypertensive medication and vice versa. BP, blood pressure. *$P < 0.05$.

### Mediating Effects of Hyperglycemia, IR, and Blood Pressure–Related Variables in Diabetes-Associated Worse Cognitive Performance

As shown in Fig. 2, differences in performance in the domains of processing speed and EF&A between individuals with type 2 diabetes and those with NGM were largely explained by hyperglycemia, with statistically significant mediating effects of 79.6% (bootstrapped 95% CI 36.6; 123.4) and 50.3% (0.6; 101.2), respectively. Differences in processing speed were also partly explained by blood pressure–related variables (mediating effect 17.7% [5.6; 30.1]), whereas IR had no mediating effects on the association of type 2 diabetes with either processing speed or EF&A. Differences in memory function were not explained by hyperglycemia or by IR or blood pressure–related variables.

Evaluation of the combined mediating effects of any combination of hyperglycemia, IR, and blood pressure–related variables (Fig. 2) suggested that the mediating effects of hyperglycemia and blood pressure are to a certain extent additive (i.e., any combination of mediators resembled the summed effects of the individual mediators). At the same time, as suggested by the multiplicative interaction that we observed between hyperglycemia and the use of antihypertensive medication, the mediating effects of hyperglycemia appeared to be more pronounced among users of antihypertensive medication compared with nonusers (data not shown). Conversely, the mediating effects of blood pressure tend to increase with the severity of hyperglycemia (data not shown).

Figure 3 shows the results obtained when the mediating effects of the individual components of the composite indices were considered. Again, diabetes-associated worse performance in processing speed and EF&A was partially explained by measures of hyperglycemia, with $HbA_{1c}$ being the most important mediator. Likewise, the use of antihypertensive medication and, to a much lesser extent, the weighted SD of diastolic blood pressure mediated a small part of the diabetes-associated differences in performance in processing speed and EF&A. For memory function, none of the individual components of any of the composite indices showed statistically significant mediating

**Table 3—Association between individual components of composite indices and cognitive performance**

| | Memory | Processing speed | EF&A |
|---|---|---|---|
| (ln) Fasting glucose (mmol/L) | −0.026 (0.163) | −0.099* (<0.001) | −0.072* (<0.001) |
| (ln) Postload glucose (mmol/L)# | −0.036 (0.057) | −0.069* (<0.001) | −0.066* (0.001) |
| $HbA_{1c}$ (%) | −0.008 (0.676) | −0.109* (<0.001) | −0.082* (<0.001) |
| SAF (AU) | −0.014 (0.436) | −0.076* (<0.001) | −0.074* (<0.001) |
| (ln) HOMA-IR (AU) | −0.031 (0.079) | −0.032 (0.062) | −0.051* (0.005) |
| 24-h Systolic blood pressure (mmHg) | −0.001 (0.953) | 0.005 (0.777) | −0.006 (0.751) |
| 24-h Diastolic blood pressure (mmHg) | −0.006 (0.754) | 0.027 (0.123) | −0.003 (0.865) |
| (ln) Weighted SD systolic blood pressure (mmHg) | 0.011 (0.546) | −0.019 (0.262) | 0.006 (0.730) |
| (ln) Weighted SD diastolic blood pressure (mmHg) | −0.011 (0.526) | −0.076* (<0.001) | −0.040* (0.024) |
| Use of antihypertensive medication (yes vs. no) | −0.085* (0.017) | −0.084* (<0.001) | −0.050* (0.008) |

*N* = 2,531. Data are presented as standardized regression coefficients (*P* values), except for the use of antihypertensive medication, where unstandardized regression coefficients (*P* values) are presented. All analyses are adjusted for age, sex, and educational level. AU, arbitrary units; ln, natural logarithm. *$P < 0.05$. #*n* = 2,388.

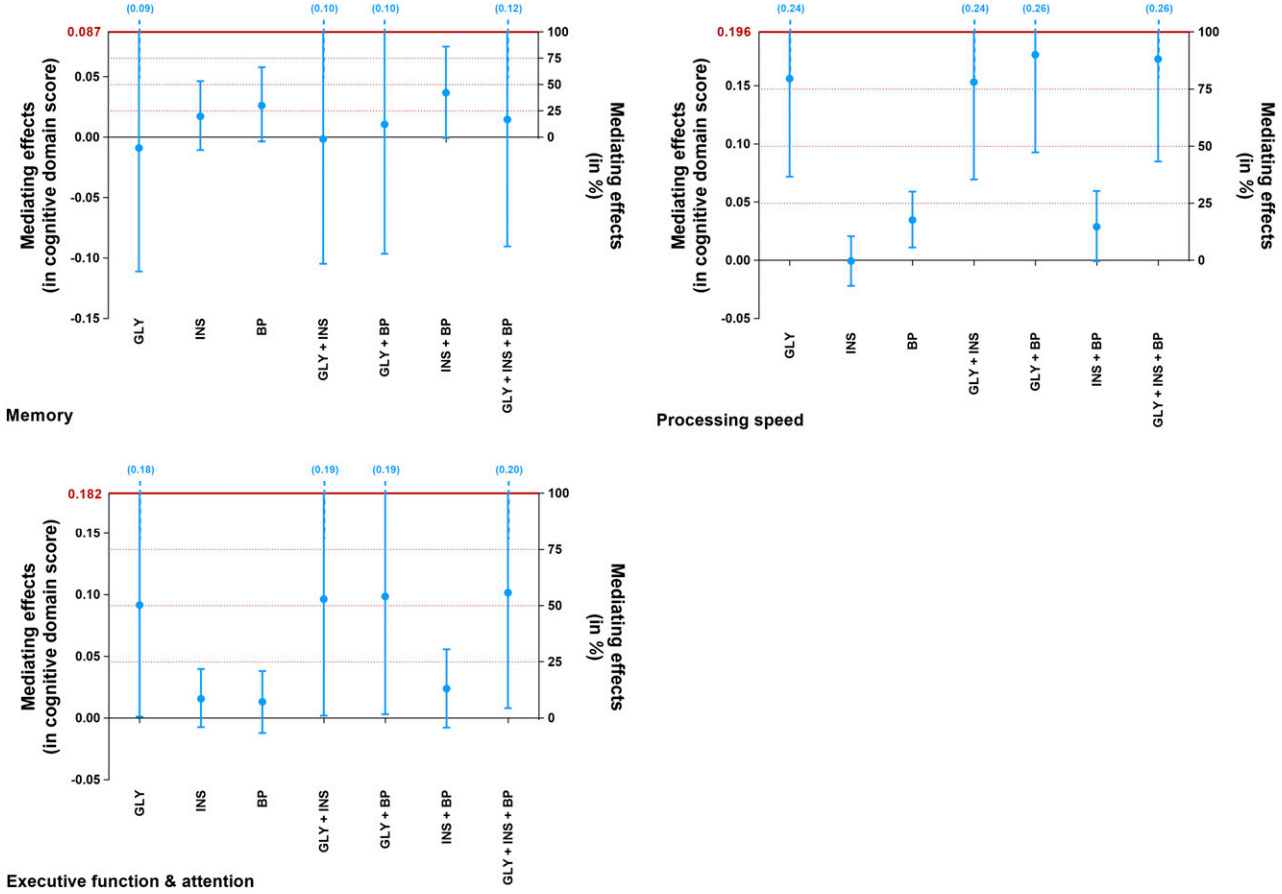


**Figure 2—**Mediating effects of hyperglycemia, IR, and blood pressure–related variables on the association between type 2 diabetes and cognitive performance. Mediating effects are presented as the indirect effects of type 2 diabetes on cognitive performance through the potential mediators (i.e., hyperglycemia, IR, and blood pressure) in cognitive domain scores (left, *y*-axis) and percentage of mediation (right, *y*-axis). All analyses are adjusted for age, sex, and educational level. The dotted red lines indicate a mediation effect of 25%, 50%, and 75%, respectively. The solid red line indicates the mean difference in cognitive domain scores between individuals with type 2 diabetes and those with a NGM, and thus corresponds with a mediation effect of 100%. BP, index that combines 24-h systolic and diastolic blood pressure and their weighted SD with the use of antihypertensive medication; GLY, composite index of fasting glucose, postload glucose, $HbA_{1c}$, and SAF (advanced glycation end products); INS, HOMA-IR.

effects. Collinearity diagnostics revealed no multicollinearity in any of the mediation analyses (i.e., all tolerance values ≥0.206 and variance inflation factors ≤4.843).

### Sensitivity Analyses

Results that were qualitatively similar to those reported above were observed when individuals with newly diagnosed type 2 diabetes were analyzed separately from those with a prior diagnosis of diabetes or when individuals treated with insulin were excluded from the analyses (data not shown). Overall, additional adjustment for prior cardiovascular disease, cardiovascular risk factors, and depression reduced diabetes-related worse cognitive performance (by 62.9% for memory function, by 13.4% for processing speed, and by 1.1% for EF&A). However, the pattern of mediation by hyperglycemia and blood pressure–related variables was comparable to that observed after adjustment for age, sex, and educational level only (Supplementary Fig. 1). Additional examination of the mediating effects of the cardiovascular risk factors themselves revealed that only waist circumference and a history of cardiovascular disease statistically significantly mediated diabetes-related worse performance in memory function and EF&A, respectively (Supplementary Fig. 2). The presence of a depression mediated (albeit marginally) diabetes-related worse performance in all the cognitive domains that were assessed (Supplementary Fig. 2). The presence of microvascular disease had a small but significant mediating effect (8.5% [bootstrapped 95% CI 0.4; 17.0]; *n* = 2,292) on the difference in processing speed between individuals with type 2 diabetes and NGM. On closer examination, this small mediating effect was mainly explained by albuminuria (5.6% [1.3; 11.2]) and disappeared once adjustments were made for hyperglycemia (data not shown).

When the composite index of hyperglycemia focused on long-term hyperglycemia, its mediating effects became somewhat smaller as did their 95% CIs, indicating more accurate estimates (Supplementary Fig. 3). Hypoglycemic events also appeared to have a significant mediating effect on differences in EF&A (27.1% [bootstrapped 95% CI 4.8; 47.8]; *n* = 2,153), although this result should be interpreted with caution because hypoglycemic events occur only in individuals with type 2 diabetes. As in the

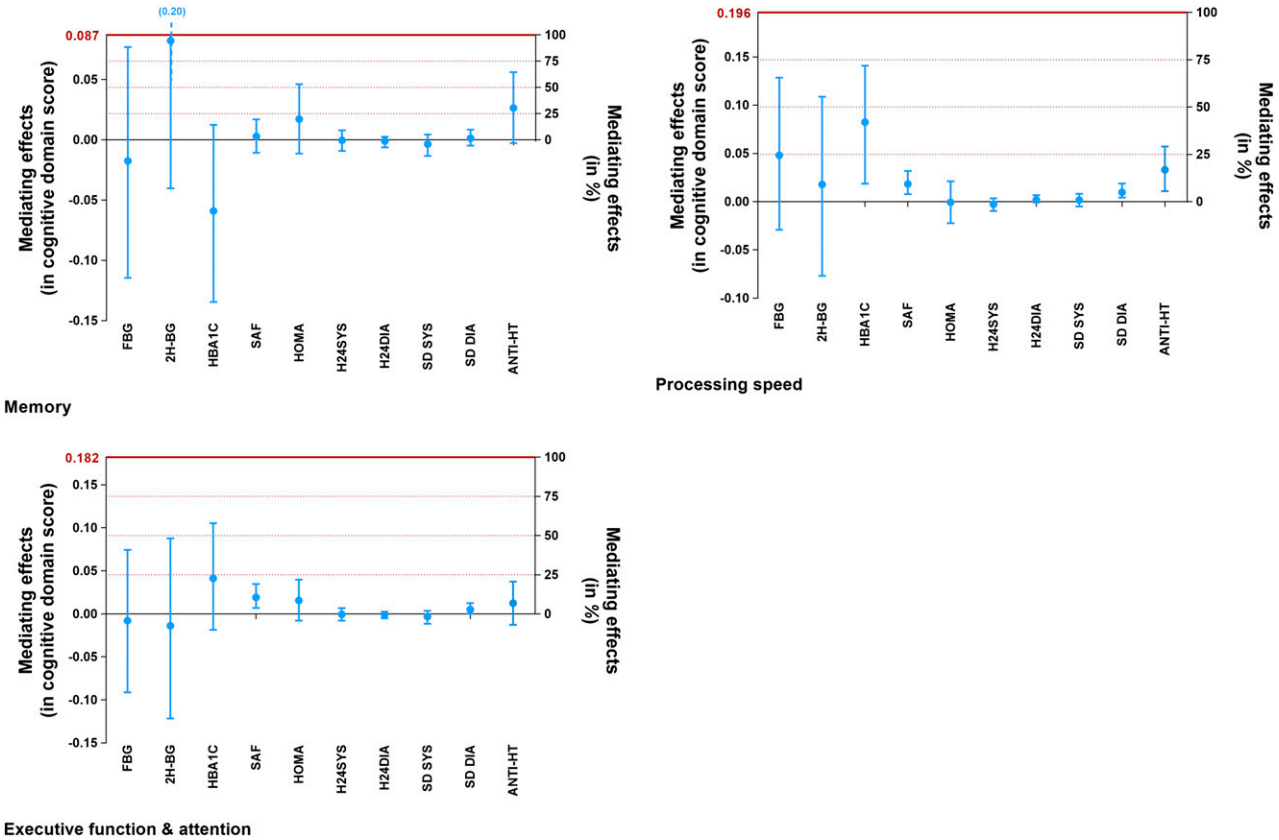


**Figure 3**—Mediating effects of individual components of hyperglycemia, IR, and blood pressure–related variables on the association between type 2 diabetes and cognitive performance. Mediating effects are presented as the indirect effects of type 2 diabetes on cognitive performance through the potential mediators in cognitive domain scores (left, *y*-axis) and percentage of mediation (right, *y*-axis). All analyses are adjusted for age, sex, and educational level. The dotted red lines indicate a mediation effect of 25%, 50%, and 75%, respectively. The solid red line indicates the mean difference in cognitive domain scores between individuals with type 2 diabetes and those with a NGM and thus corresponds with a mediation effect of 100%. ANTI-HT, use of antihypertensive medication; FBG, fasting blood glucose; H24DIA, mean 24-h diastolic blood pressure; H24SYS, mean 24-h systolic blood pressure; SD DIA, weighted SD of 24-h diastolic blood pressure; SD SYS, weighted SD of 24-h systolic blood pressure; 2H-BG, postload glucose.

main analysis, IR had no mediating effects when defined in multiple alternative ways (Supplementary Fig. 4). Results were also very similar when 24-h pulse pressure rather than systolic and diastolic blood pressure was incorporated into the index of blood pressure abnormalities (Supplementary Fig. 5). Importantly, however, blood pressure lost its mediating effects when the use of antihypertensive medication was excluded from the index of blood pressure–related variables (Supplementary Fig. 6).

## CONCLUSIONS

In the current study, diabetes-associated worse performance in the domains of processing speed and EF&A was largely explained by hyperglycemia and, to a lesser extent, by blood pressure–related variables, whereas IR had no mediating effects. Comparable results were obtained after adjustment for additional cardiovascular risk factors such as waist circumference and dyslipidemia. As such, our findings indicate that it is the glycemic load itself, rather than the cardiovascular context in which diabetes typically develops, that contributes to the differences in cognitive performance between individuals with relatively well-controlled type 2 diabetes and those with NGM.

The observed profile of diabetes-related differences in cognitive performance is consistent with that of mild differences across multiple domains reported in previous systematic reviews (32,33). For memory function, however, relatively smaller differences were observed than have been previously reported. It has been suggested that a diminished ability to process unstructured information is the primary deficit underlying diabetes-associated cognitive problems and thus may precede memory deficits (34). This, combined with specific characteristics of our population with diabetes (i.e., generally well-controlled $HbA_{1c}$ level and relatively highly educated), may have limited our ability to assess the extent to which diabetes impacts memory function as did the use of a single test to assess memory function. Characteristics of the study population may also explain the lack of reduced cognitive performance in individuals with prediabetes, although we observed a trend of decreasing cognitive abilities with worsening glucose metabolism.

We are the first to show that hyperglycemia largely explains diabetes-associated worse cognitive performance, which is in line with the results of a recent study (35) that demonstrated that SAF partially mediates the association of type 2 diabetes with reduced gray matter volume. From a pathophysiological point of view, intracellular hyperglycemia induces

mitochondrial overproduction of superoxide (36), which, in turn, activates multiple pathways through which hyperglycemia could exert toxic effects on the brain either directly, by triggering neuronal dysfunction and cell death (37), or indirectly, by inducing microvascular and/or macrovascular changes (26,38,39).

The mediating role of hyperglycemia that was observed seems to contrast with findings of our recent systematic review (40), where we showed that measures of hyperglycemia are only weakly associated with cognitive performance among individuals with type 2 diabetes. This pattern is, however, remarkably similar to that observed for some classic complications of diabetes in that previous studies have shown that glycemic control is more closely related to the development than to the progression of nephropathy (41) and retinopathy (42). It is possible that hyperglycemia sets the stage for other (organ-specific) mechanisms to exert their detrimental effects, an explanation that is supported by our observation of interaction between hyperglycemia and the use of antihypertensive medication in their association with cognitive performance. Alternatively, one might argue that the mediating effects we observed simply reflect the collinearity between our composite index of hyperglycemia and participants' glucose metabolism status. Collinearity statistics did not, however, reveal any problematic multicollinearity and qualitatively similar mediating effects were obtained when the composite index of hyperglycemia focused on long-term hyperglycemia.

The current study provides evidence that abnormalities in blood pressure also contribute to diabetes-associated differences in processing speed, although to a lesser extent than hyperglycemia. Sensitivity analyses, however, showed that these mediating effects were mainly attributable to the use of antihypertensive medication and thus to previous exposure to elevated blood pressure levels rather than the actual blood pressure. Conversely, the frequent use of antihypertensive medication among individuals with type 2 diabetes, which is likely to have contributed to the small differences in 24-h blood pressure observed between individuals with different glucose metabolism (i.e., $<$5 mmHg), may have limited our ability to adequately assess the mediating effects of actual blood pressure in diabetes-associated differences in cognitive performance.

Although our data suggest that IR does not contribute to diabetes-related worse cognitive performance, and, despite the fact that this was confirmed through a range of sensitivity analyses, this finding should be interpreted with some caution. Apart from the fact that we used surrogate markers of IR (e.g., HOMA-IR), these markers typically reflect hepatic and muscle IR, although it has been suggested that these do not necessarily coincide with cerebral IR (43). Consequently, we cannot fully exclude the possibility of cerebral IR being involved in diabetes-associated cognitive decrements.

The current study has some further limitations. First, its cross-sectional design does not permit us to draw firm conclusions about the etiology of diabetes-associated worse cognitive performance. Second, the generalizability of our findings can be questioned because individuals with type 2 diabetes in our cohort were generally well controlled for their diabetes and comorbid vascular risk factors. Individuals were, however, not selected on the basis of their glycemic control, and hence we believe our population is representative of a population that has access to quality diabetes care. Third, despite the fact that we used sensitive tests to assess cognitive performance in the domains most frequently reported to be affected in diabetes (33), we were unable to capture all the cognitive domains that might be important for daily functioning and patient well-being. Moreover, as acknowledged above, our composite *z* score for memory function was based on a single and relatively simple memory test. Last, we focused on hyperglycemia but missed data on glucose variability, which is increasingly recognized to be associated with diabetes complications.

In conclusion, our findings indicate that differences in cognitive performance between individuals with type 2 diabetes and those with NGM, particularly in the domains of processing speed and EF&A, are largely attributable to hyperglycemia and, to a lesser extent, to blood pressure–related variables, whereas IR has no mediating effects. Although the cognitive decrements we observed are unlikely to cause clinically manifest neurocognitive symptoms, they may lead to complaints of forgetfulness and concentration loss, highlighting the need for preventive strategies and neuropsychological training or counseling. We believe that our findings suggest that the prevention of diabetes-associated decrements in cognitive performance should focus on early glycemic and blood pressure control, that is, before the diabetes becomes apparent. As such, our data add fuel to the debate as to whether individuals with prediabetes should be monitored and treated more intensively.

**Funding.** The research of G.J.B. is supported by grant 2010T073 from the Dutch Heart Association, and S.L.C.G. and G.J.B. are supported by Vidi grant 91711384 from ZonMw, The Netherlands Organisation for Health Research and Development. The Maastricht Study was supported by the European Regional Development Fund via OP-Zuid; the Province of Limburg; the Dutch Ministry of Economic Affairs (grant 31O.041); Stichting De Weijerhorst (Maastricht, the Netherlands); the Pearl String Initiative Diabetes (Amsterdam, the Netherlands); the Cardiovascular Center (Maastricht, the Netherlands); Cardiovascular Research Institute Maastricht (Maastricht, the Netherlands); School for Public Health and Primary Care (Maastricht, the Netherlands); School for Nutrition, Toxicology and Metabolism (Maastricht, the Netherlands); Stichting Annadal (Maastricht, the Netherlands); Health Foundation Limburg (Maastricht, the Netherlands); and unrestricted grants from Janssen-Cilag B.V. (Tilburg, the Netherlands), Novo Nordisk Farma B.V. (Alphen aan den Rijn, the Netherlands), and Sanofi-Aventis Netherlands B.V. (Gouda, the Netherlands).

Note that none of the funders had any role in study design; the collection, analysis, and interpretation of the data; the writing of the manuscript; or the decision to submit the paper for publication.

**Duality of Interest.** G.J.B. consults for and receives research support from Boehringer Ingelheim, consults for Takeda Pharmaceuticals, and has received speaker's fees from Eli Lilly. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** S.L.C.G. was involved in study conception and design, participated in data acquisition and cleaning, analyzed and interpreted the data, and prepared the manuscript. S.J.S.S. and C.D.A.S. were involved in study conception and design, contributed to the interpretation of the data, critically revised the manuscript for intellectual content, and were responsible for data acquisition. D.C. contributed to the interpretation of the data and critically revised the manuscript for intellectual content. M.T.S., M.P.J.v.B., R.M.A.H., F.R.J.V., A.A.K., P.C.D., C.G.S., and C.J.H.v.d.K. were responsible for data acquisition and also critically reviewed the manuscript for intellectual content. G.J.B. was involved in study conception and design, contributed to interpretation of the data, and critically revised the manuscript for intellectual content. All authors approved the final version

of this manuscript. S.L.C.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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