Both Low and High 24-Hour Diastolic Blood Pressure Are Associated With Worse Cognitive Performance in Type 2 Diabetes: The Maastricht Study

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OBJECTIVE

Hypertension and diabetes are both risk factors for cognitive decline, and individuals with both might have an especially high risk. We therefore examined linear and nonlinear (quadratic) associations of 24-h blood pressure (BP) with cognitive performance in participants with and without type 2 diabetes. We also tested the association of nocturnal dipping status with cognitive performance.

RESEARCH DESIGN AND METHODS

This study was performed as part of the Maastricht Study, an ongoing population-based cohort study. Cross-sectional associations of 24-h BP (n = 713, of whom 201 had type 2 diabetes) and nocturnal dipping status (n = 686, of whom 196 had type 2 diabetes) with performance on tests for global cognitive functioning, information processing speed, verbal memory (immediate and delayed word recall), and response inhibition were tested using linear regression analysis and adjusted for demographics, vascular risk factors, cardiovascular disease, depression, and lipid-modifying and antihypertensive medication use.

RESULTS

After full adjustment, we found quadratic (inverted U-shaped) associations of 24-h diastolic blood pressure (DBP) with information processing speed (b for quadratic term = −0.0267, $P < 0.01$) and memory (immediate word recall: b = −0.0180, $P < 0.05$; delayed word recall: b = −0.0076, $P < 0.01$) in participants with diabetes, but not in those without. No clear pattern was found for dipping status.

CONCLUSIONS

This study shows that both low and high 24-h DBP are associated with poorer performance on tests of information processing speed and memory in individuals with type 2 diabetes.

Type 2 diabetes is associated with cognitive decline and dementia (1,2), but the pathological mechanisms underlying these associations are not yet clear. Proposed mechanisms include the role of vascular risk factors, such as hypertension. Some studies have shown an association of hypertension with cognitive dysfunction and Alzheimer disease in individuals with diabetes (3,4). In addition, diabetes and hypertension seem to interact in their effect on cognitive decline (5) and dementia (6),

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indicating that individuals with both diabetes and hypertension may have an especially high risk of cognitive decline. Other studies, however, did not confirm these results (7,8).

Above-mentioned studies (5–8) used office measurements as an estimate of blood pressure (BP) exposure. However, office BP measurement is less accurate than 24-h ambulatory BP measurement (ABPM) and cannot capture important physiological phenomena such as the normal decrease of BP during sleep (so-called "dipping"). Indeed, ambulatory BP has shown to be superior to office BP in predicting progression of cerebrovascular disease and cognitive decline (9). In addition, nondipping, i.e., the blunting of the physiological BP reduction during sleep, as well as extreme dipping, i.e., excessive reduction in BP during sleep, have been associated with cerebrovascular damage and lower cognitive performance (10–12). Nondipping is more prevalent in type 2 diabetes (13), and as both diabetes and abnormal dipping patterns have been associated with lower cognitive performance, one may speculate that individuals with diabetes who show abnormal dipping in nocturnal BP are especially at risk to develop cognitive impairment.

To our knowledge, there are no studies to date that have addressed the question of whether ambulatory BP and dipping parameters are associated with multiple cognitive domains in type 2 diabetes. Therefore, we studied associations between 24-h ambulatory BP and cognitive performance stratified by diabetes status. Since previous studies have shown quadratic relationships between BP and cognitive functions (14,15), we examined both linear and quadratic associations. In addition, we examined the association of nondipping and extreme dipping in BP during sleep with cognitive performance in individuals with and without type 2 diabetes. Based on the above, we hypothesized that associations between 24-h ambulatory BP, nondipping, and extreme dipping on the one hand and cognitive functions on the other are stronger in individuals with type 2 diabetes compared with those without diabetes.

RESEARCH DESIGN AND METHODS

Study Population and Design

In this study, we used data from the Maastricht Study, an observational, prospective, population-based cohort study. The rationale and methodology have been described previously (16). In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of type 2 diabetes and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known type 2 diabetes status for reasons of efficiency. The present report includes cross-sectional data from the first 866 participants, who completed the baseline survey between November 2010 and March 2012. The examinations of each participant were performed within a time window of 3 months. The study has been approved by the institutional medical ethics committee (NL31329.068.10) and the Netherlands Health Council under the Dutch "Law for Population Studies" (permit 131088-105234-PG). All participants gave written informed consent.

Glucose Metabolism Status

To determine glucose metabolism, all participants (except those who use insulin) underwent a standardized 7-point oral glucose tolerance test after an overnight fast as previously described (16). Glucose metabolism was defined according to the World Health Organization 2006 criteria into normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes (17). Additionally, individuals without type 1 diabetes and on diabetes medication were considered as having type 2 diabetes (16). For this study, we defined having either IFG or IGT as impaired glucose metabolism (IGM).

ABPMs

Ambulatory BP was measured with ambulatory 24-h BP monitoring (WatchBP O3; Microlife AG, Widnau, Switzerland). Cuffs were applied to the participants' nondominant arm. Measurements were programmed for every 15 min during daytime (08:00 A.M.–11:00 P.M.) and every 30 min during the night (11:00 P.M.–08:00 A.M.), for a total of 24 h. As quality criteria, mean 24-h BP measurements were only calculated if there were >14 valid measurements at daytime and >7 valid measurements at night, based on recommendations of the British Hypertension Society (18,19). Mean 24-h systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated based on hourly averages (20). Twenty four–hour pulse pressure (PP) was defined as 24-h SBP minus 24-h DBP and mean arterial pressure (MAP) as 24-h DBP plus (0.412 × 24-h PP) (21). Mean daytime and nighttime SBP and DBP were calculated using measurements between 09:00 A.M. and 09:00 P.M. (>14 valid measurements were required) and between 01:00 A.M. and 06:00 A.M. (>7 valid measurements were required), respectively (18). The relative difference between mean daytime and mean nighttime BP levels was computed and expressed as a percentage of the daytime BP average. Participants were classified as nondippers when the nocturnal drop in SBP or DBP was <10% of the mean daytime level and as extreme dippers when the nocturnal drop was ≥20% (22). In all other cases, participants were assigned to the dipper category.

Assessment of Cognitive Function

A concise battery (30 min) of cognitive tests was used to assess cognitive functioning (16). An a priori selection of these cognitive tests was used in the current study. Global cognitive functioning was measured by the Mini-Mental State Examination (23). Verbal memory was assessed with the Visual Verbal Word Learning Test (24). In this test, 15 words are presented in five subsequent trials, followed by a recall phase immediately after each trial (immediate recall) and a delayed recall phase 20 min thereafter (delayed recall). Response inhibition was measured with the Stroop Color Word Test (25,26). The variable of interest was the interference measure expressed in seconds. The Letter-Digit Substitution Test (27) was used to measure information processing speed. Participants were instructed to match digits to letters as quickly as possible within 90 s.

Covariates

History of cardiovascular disease, diabetes duration, smoking status (never, former, or current), and alcohol consumption were assessed by questionnaire (16,28). Alcohol consumption was classified into three categories as described elsewhere (28). Lipid-modifying, antihypertensive, and glucose-lowering medication use were assessed during a medication

interview where generic name, dose, and frequency were registered (16). Waist circumference, glycosylated hemoglobin A_{1c} (HbA_{1c}), total and HDL cholesterol, creatinine, and triglycerides were determined as described elsewhere (16). Estimated glomerular filtration rate (eGFR) was estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation based on serum creatinine (29). Vibration perception thresholds (VPTs) were tested with a Horwell Neurothesiometer (Scientific Laboratory Supplies, Nottingham, U.K.) in order to assess the presence of nerve damage due to diabetic neuropathy. VPTs were tested three times at the distal phalanx of the hallux of the right and left foot (16). We used the mean value of the two feet for analyses. Level of education was assessed during the cognitive assessment and was classified into eight categories commonly used in the Netherlands (30). Three groups were made for educational level: low (level 1–3), intermediate (level 4–6), and high (level 7–8) (28). Presence of depression was assessed by the Mini International Neuropsychiatric Interview (16,31).

Statistical Analysis

Analyses were conducted using SPSS version 20 for Mac OSX (SPSS, Inc.). Differences between group characteristics were tested using independent samples Student *t* test for continuous variables and χ^2 tests for categorical variables. Multiple linear regression analysis was used to estimate the association between ambulatory BP and cognitive performance, stratified by diabetes status. Both linear and quadratic (squared) 24-h BP terms were included in the models. To control for multicollinearity, linear terms were centered around the mean before forming the quadratic term by subtracting the mean value of the sample from the raw values. When the quadratic term was not significantly associated with any cognitive measure, it was dropped from the models. For analyses with dipping status, three groups were made: dippers (reference group), nondippers, and extreme dippers (see above). Associations were first adjusted for age, sex, and educational level (model 1), and then for smoking, alcohol, waist circumference, total cholesterol-to-HDL cholesterol ratio, triglyceride level, antihypertensive medication use, lipid-modifying medication use, eGFR, cardiovascular disease, and depression (model 2). Response inhibition scores were log transformed before regression analysis because they were positively skewed. A two-sided *P* value of <0.05 was considered statistically significant.

RESULTS

Of the 866 participants included in the Maastricht Study, four individuals with type 1 diabetes and four participants who did not have a cognitive assessment were excluded. Of the remaining 858 participants, we additionally excluded individuals with missing data on the independent variables, i.e., 24-h BP (n = 88) and dipping parameters (n = 116), or with missing data on the potential confounders (n = 57). This resulted in 713 participants (512 without and 201 with diabetes) for analyses with 24-h BP and 686 participants (490 without and 196 with diabetes) for dipping variables. Participants who were excluded due to missing values were more often low educated and more likely to be depressed, to be current smokers, and to use glucose-lowering medication (particularly insulin). There were no differences in other baseline characteristics (data not shown).

Table 1 shows the general characteristics of the 713 individuals included stratified by diabetes status. Of these, 201 participants (28.2%) had type 2 diabetes, of whom 32 (15.9%) were newly diagnosed at study entry, 119 (59.2%) used oral medication (of whom 2 participants also used glucagon-like peptide 1 receptor agonists) and 37 (18.4%) used insulin (of whom 27 also used oral medication).

Of the 512 participants without diabetes, 118 participants (16.5% of the total sample) had IGM. There were no significant differences in performance on any cognitive measure between participants with IGM and those with NGT after adjustment for age and sex ($P >$ 0.10 for all measures) (data not shown).

Twenty Four–Hour SBP, DBP, and Cognitive Performance

Table 2 shows adjusted linear and quadratic associations between 24-h BP and cognitive measures. In participants without diabetes, no significant linear or quadratic associations between 24-h SBP or DBP and cognitive measures were observed (Table 2, models 1 and 2). In participants with type 2 diabetes, no linear or quadratic associations were found between 24-h SBP and cognitive performance after adjustment for potential confounders (models 1 and 2). However, 24-h DBP showed quadratic associations with information processing speed, immediate and delayed recall, and response inhibition in model 1 (Table 2). After full adjustment, these associations remained significant, except for response inhibition (P = 0.074). These associations indicated that individuals with diabetes and either a low or high 24-h DBP performed more poorly on tasks for speed, as well as for immediate and delayed word recall, than those with a midrange DBP (an inverted U-shaped relation). Additional analyses showed that associations of 24-h SBP and DBP with cognitive performance were similar in participants with IGM and NGT (data not shown).

Furthermore, quadratic associations of 24-h DBP with information processing speed and memory were significantly different in participants with diabetes compared with those without, for information processing speed (P for interaction between diabetes and quadratic 24-h DBP = 0.001), immediate word recall (P for interaction = 0.021), and delayed word recall (P for interaction = 0.009) in the fully adjusted model (model 2). These interactions are depicted in Fig. 1.

Further analyses of daytime (available for 495 participants without and 198 with diabetes) and nighttime (available for 500 participants without and 197 with diabetes) SBP and DBP separately showed no significant linear or quadratic associations of daytime or nighttime SBP with cognitive performance in individuals without diabetes after full adjustment for potential confounders (data not shown). In individuals with diabetes, we found a linear association between daytime SBP and information processing speed ($P < 0.05$), but no other significant associations. In contrast, both quadratic daytime and quadratic nighttime DBP were significantly associated with information processing speed, and immediate and delayed word recall ($P < 0.05$) after full adjustment for potential confounders in individuals with diabetes, but not in those without (data not shown).

Twenty Four–Hour PP, MAP, and Cognitive Performance

In participants without diabetes, neither 24-h PP nor 24-h MAP was significantly

Table 1—Baseline characteristics of the 713 participants stratified by diabetes status

Characteristic	No T2D (*n* = 512)	T2D (*n* = 201)	*P* value*
Age, mean (SD)	58.3 (8.5)	63.7 (7.0)	<0.001
Male sex, *n* (%)	248 (48.4)	145 (72.1)	<0.001
Educational level, low/middle/high, *n* (%)	57/201/254 (11.1/39.3/49.6)	52/102/47 (25.9/50.7/23.4)	<0.001
Smoking status, never/former/current, *n* (%)	180/257/75 (35.2/50.2/14.6)	43/132/26 (21.4/65.7/12.9)	0.001
Alcohol consumption, none/low/high, *n* (%)	65/275/172 (12.7/53.7/33.6)	57/103/41 (28.4/51.2/20.4)	<0.001
Waist circumference (cm), mean (SD)	93.6 (11.8)	106.0 (13.0)	<0.001
Total cholesterol-to-HDL cholesterol ratio, mean (SD)	4.24 (1.29)	4.15 (1.10)	0.34
Triglycerides (mmol/L), median (IQR)	1.13 (0.79–1.58)	1.63 (1.12–2.27)	<0.001**
Antihypertensive medication use, *n* (%)	141 (27.5)	138 (68.7)	<0.001
Lipid-modifying medication, *n* (%)	100 (19.5)	157 (78.1)	<0.001
HbA_{1c} (%), mean (SD)	5.7 (0.4)	6.9 (0.8)	<0.001
HbA_{1c} (mmol/mol), mean (SD)	38.3 (4.0)	51.8 (8.8)	<0.001
Glucose-lowering medication use, none/oral/insulin, *n* (%)	—	45/119/37 (22.4/59.2/18.4)	
Diabetes duration (years), median (IQR)	—	7 (3.0–11.0)	
eGFR (mL/min/1.73 m^2), mean (SD)	85.7 (14.1)	82.5 (15.0)	0.01
VPT (V), median (IQR)§	9.2 (6.3–13.5)	13.4 (9.8–20.8)	<0.001**
Cardiovascular disease, *n* (%)	63 (12.3)	61 (30.3)	<0.001
Depression, *n* (%)	15 (2.9)	11 (5.5)	0.10
SBP 24 h (mmHg), mean (SD)	117.7 (11.9)	123.7 (12.8)	<0.001
DBP 24 h (mmHg), mean (SD)	74.2 (7.3)	73.9 (7.2)	0.58
PP 24 h (mmHg), mean (SD)	43.5 (8.0)	49.8 (10.3)	<0.001
MAP 24 h (mmHg), mean (SD)	92.2 (8.6)	94.4 (8.5)	0.002
Dipper status SBP, dippers/nondippers/extreme dippers, *n* (%)	258/174/58 (52.7/35.5/11.8)	91/89/16 (46.4/45.4/8.2)	0.04
Dipper status DBP, dippers/nondippers/extreme dippers, *n* (%)	212/56/222 (43.3/11.4/45.3)	72/52/72 (36.7/26.5/36.7)	<0.001
Global cognitive functioning (score), mean (SD)	29.1 (1.1)	28.5 (1.4)	<0.001
Information processing speed (number of digits), mean (SD)	50.4 (9.1)	44.2 (8.8)	<0.001
Immediate word recall (number of words), mean (SD)	47.2 (9.2)	40.7 (9.4)	<0.001
Delayed word recall (number of words), mean (SD)	10.0 (2.8)	8.4 (2.9)	<0.001
Response inhibition (s), median (IQR)	39.2 (30.8–49.7)	52.2 (38.8–70.3)	<0.001**

For global cognitive functioning, information processing speed, immediate word recall, and delayed word recall, higher scores indicate better performance. For response inhibition, lower scores indicate better performance. T2D, type 2 diabetes. **P* for difference between groups. ***P* values are derived from independent samples Student *t* tests with log-transformed outcomes. §Available for 381 participants without diabetes and 142 with diabetes.

associated with cognitive performance (Supplementary Table 1). In participants with diabetes, we found no significant associations between 24-h PP and cognitive measures, but the quadratic term of 24-h MAP was significantly associated with information processing speed (model 1: b for quadratic term = −0.0159, *P* = 0.004; model 2: b = −0.0126, *P* = 0.026). The quadratic association of 24-h MAP with delayed word recall was significant in model 1 (b = −0.0039, *P* = 0.040) but became nonsignificant after full adjustment (b = −0.0035, *P* = 0.069). The quadratic association with immediate word recall was not significant (model 1: b = −0.0108, *P* = 0.077; model 2: b = −0.0064, *P* = 0.294). Since another calculation of MAP (24-h DBP + 1/3 * [24-h SBP − 24-h DBP]) has been used previously in other studies, we performed additional analyses with this definition of MAP. Results showed that the quadratic association of 24-h MAP with delayed word recall increased slightly and became significant in participants with diabetes (model 2: b = −0.0042, *P* = 0.042). Other associations remained largely unchanged (data not shown).

Dipping and Cognitive Performance

Supplementary Table 2 shows the results of the associations between dipping status and cognitive performance stratified by diabetes status. In participants without diabetes, nondipping in DBP was associated with slower information processing speed after full adjustment for potential confounders (model 2: b = −2.713, *P* = 0.029). Other dipping parameters were not associated with cognitive performance (Supplementary Table 2). In participants with diabetes, extreme dipping in SBP was associated with worse global cognitive functioning (model 2: b = −0.973, *P* = 0.012). Extreme dipping in DBP was associated with a decreased delayed word recall in participants with diabetes, but only after full adjustment

Table 2—Associations (regression coefficients) of 24-h SBP and DBP with cognitive performance, stratified by diabetes status

	Global cognitive functioning		Information processing speed		Immediate word recall		Delayed word recall		Response inhibition#	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
No diabetes										
24-h SBP§										
Linear	0.0027	0.0041	0.0348	0.0356	0.0206	0.0391	0.0075	0.0087	−0.0005	−0.0006
24-h DBP§										
Linear	−0.0013	0.0011	0.0485	0.0514	−0.0042	0.0338	−0.0035	0.0030	0.0000	−0.0003
Diabetes										
24-h SBP§										
Linear	−0.0034	−0.0043	−0.0700	−0.0846	0.0356	0.0329	0.0103	0.0091	0.0008	0.0014
24-h DBP										
Linear	0.0190	0.0160	0.0235	0.0188	0.1361	0.1062	0.0512	0.0556	−0.0024	−0.0019
Quadratic	−0.0014	−0.0007	−0.0314**	−0.0267**	−0.0253**	−0.0180*	−0.0085**	−0.0076**	0.0004*	0.0003

For global cognitive functioning, information processing speed, and immediate and delayed word recall, a higher score indicates better performance, and for response inhibition, a lower score indicates better performance. Model 1, adjustment for age, sex, and educational level; model 2, model 1 + adjustment for smoking status, alcohol consumption, waist circumference, total cholesterol-to-HDL cholesterol ratio, triglyceride level, antihypertensive medication use, lipid-modifying medication use, eGFR, cardiovascular disease, and depression. §For these associations, the quadratic term was not significantly associated with any cognitive measure and was therefore dropped from the models. #Scores are log transformed. *$P < 0.05$. **$P < 0.01$.

for confounders (model 2: b = −0.928, $P = 0.038$).

Post Hoc Analyses

We further adjusted the significant quadratic associations of 24-h DBP with information processing speed, and immediate and delayed word recall in participants with diabetes for the diabetes-related variables HbA_{1c} level, diabetes duration (available for 168 individuals with diabetes), and glucose-lowering medication use (yes/no) (data not shown). These associations did not change after further adjustment. Since diabetic neuropathy may affect associations of BP with cognitive performance, we also adjusted these associations in a separate model for VPTs (available for 142 individuals with diabetes) as a marker for nerve damage due to diabetic neuropathy. Additional adjustment for VPTs (model 2 + adjustment for VPTs) did not materially change the associations (data not shown).

Last, we examined associations of 24-h SBP and DBP variability, measured by the weighted 24-h SD (i.e., the mean of the daytime and nighttime SD, each weighted for the duration of day and night periods, respectively) (32), with cognitive performance. Mean weighted 24-h SD of SBP and DBP were significantly higher in the group with diabetes (mean weighted 24-h SD of SBP [SD] = 12.5 mmHg [3.1]; mean weighted 24-h SD of DBP [SD] = 9.8 mmHg [2.9]) compared with the group without diabetes (mean weighted 24-h SD of SBP [SD] = 11.5 mmHg [3.0]; mean weighted 24-h SD of DBP [SD] = 9.0 mmHg [2.6]) ($P <$ 0.01 for both). No significant linear or quadratic associations between weighted 24-h SBP SD and cognitive performance were observed in either group (Supplementary Table 3). We found a linear association between weighted 24-h DBP SD and global cognitive functioning in the group without diabetes, but no other significant associations in either group (Supplementary Table 3).

Sensitivity Analyses

Z scores for 24-h DBP were calculated for the group with diabetes. Participants with *z* scores >3 or <−3 were excluded from analyses to examine whether our results were influenced by extreme observations. One participant had a *z* score >3 but exclusion of this participant did not change the results (data not shown).

CONCLUSIONS

In this study, individuals with type 2 diabetes with either a low or high 24-h DBP performed worse on cognitive tests of information processing speed and verbal memory compared with those with a midrange 24-h DBP (inverted U-shaped relationship), whereas these associations were not found in individuals without diabetes. These associations were also found for both daytime and nighttime diastolic BP, separately. In contrast, we found no associations of 24-h SBP with cognitive performance and no consistent associations of 24-h BP variability with cognitive performance in either group. In addition, we found no significant associations of daytime and nighttime SBP with cognitive performance, except for a linear association between daytime SBP and information processing speed in individuals with diabetes. Finally, dipping status was associated with some measures of cognitive performance in both individuals with and without diabetes, but no clear pattern could be found in these associations.

U-shaped relationships between DBP and cognitive function have been shown previously (14,15). Moreover, both low and high office DBP and MAP, but not SBP and PP, have been associated with cognitive impairment 20 years later (15). Explanations for this U-shaped relationship may include antihypertensive medication use, arterial stiffness, atherosclerosis, and/or cerebral autoregulation.

In individuals untreated for hypertension, a high office DBP has been associated with hippocampal atrophy, whereas in those treated for hypertension, a low DBP has been associated with more hippocampal and amygdalar atrophy (33). This may indicate that antihypertensive medication use is involved in the association between DBP and cognitive performance. However, in our study, the U-shaped associations in the group with diabetes were attenuated only slightly and

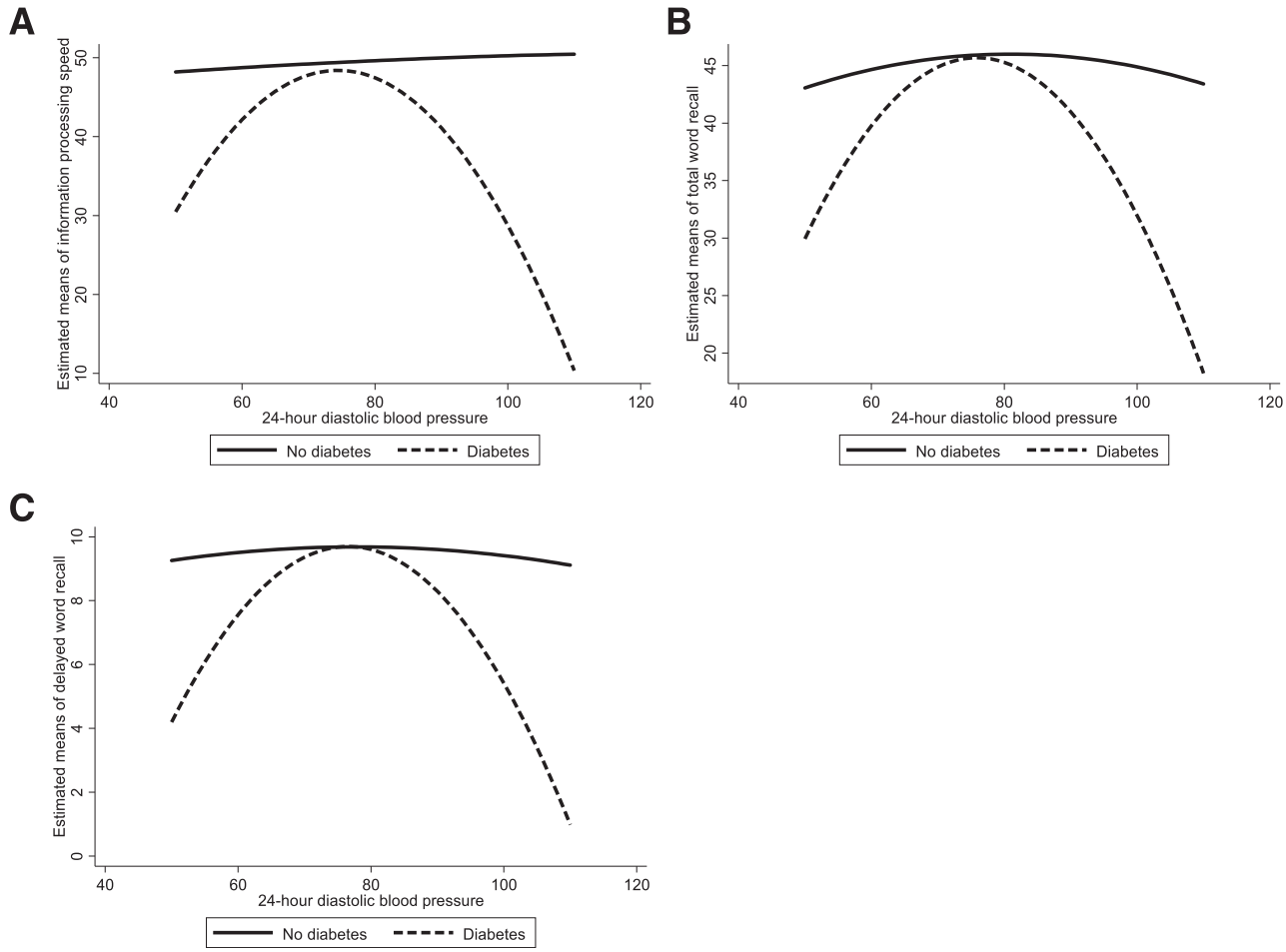

Figure 1—Interaction of nonlinear (quadratic) 24-h DBP (mmHg) and diabetes (solid, no diabetes; dash, diabetes) for information processing speed (number of digits) (*A*), immediate word recall (number of words) (*B*), and delayed word recall (number of words) (*C*).

remained significant when antihypertensive medication use was added separately to the model in addition to age, sex, and educational level (data not shown).

Another explanation may involve arterial stiffening, which is increased in individuals with type 2 diabetes (34), decreases DBP (35), and, together with atherosclerosis (36), may cause hypoperfusion of the brain, resulting in a decline in cognitive functions. However, in our study, higher 24-h PP was not related to information processing speed or memory, arguing against the possibility that arterial stiffening (which typically increases PP) explains our results.

Finally, cerebral autoregulation may be involved in the U-shaped relationship between 24-h DBP and cognitive performance. Under normal conditions, cerebral blood flow is kept constant across a wide range of MAP (60–150 mmHg) by cerebral autoregulation, which means that arterioles in the brain constrict when SBP rises and dilate when BP falls (37,38). However, in individuals with type 2 diabetes, the ability to dilate blood vessels may be decreased or even lost (39), which may be attributable to cerebral small vessel disease (39) or cardiovascular autonomic neuropathy (40). When autoregulation is lost, cerebral blood flow becomes dependent on the MAP in a linear fashion (41), and thus decline in BP can lead to hypoperfusion of the brain and consequently cognitive decline. Our finding that a low 24-h MAP was associated with decreased cognitive performance, particularly information processing speed, in individuals with diabetes fits well with this hypothesis, although this has to be confirmed by future (longitudinal) studies. In addition, orthostatic hypotension, which has been associated with diabetes (42), may have an impact on cognitive function (43), possibly by recurrent drops in (cerebral) BP. As data on cardiovascular autonomic neuropathy were not available, we could not further explore the role of autonomic neuropathy in the association of 24-h BP with cognition.

In the current study, a high DBP was also associated with poorer cognitive performance in participants with diabetes. Previous research has already shown that in individuals with type 2 diabetes, a higher DBP, but not SBP, is associated with cognitive decline (44), and that cognitive impairment is associated with cerebral small vessel disease (45). Furthermore, high DBP has shown to be an independent predictor of white matter hyperintensity progression (46) and hippocampal atrophy (33). In view of these considerations, it may be hypothesized that a high DBP leads to cognitive impairment through the development of cerebral small vessel disease. Individuals with type 2 diabetes may then be particularly susceptible to the effects of high

DBP as they are already at risk to develop cerebral small vessel disease and cognitive impairment.

We could not detect a clear pattern in the associations of nondipping and extreme dipping with aspects of cognitive performance in participants with and without diabetes. Previous studies, although not stratified by diabetes status, have shown inconsistent results with regard to the association of dipping parameters with cognitive performance and cerebrovascular damage (11,47,48). These inconsistencies may be due to differences in age, hypertensive status, and duration of hypertension and treatment history, of which reliable information can be difficult to obtain (47). Stronger associations may be found in older individuals with a long history of hypertension, and especially in older individuals with diabetes, who may have an increased risk of developing cognitive impairment. However, we acknowledge that our sample sizes of the nondipping and extreme dipping groups were quite small, which limits the power to find significant associations. Finally, it has been suggested that repeated ABPM may increase the accuracy of dipper status assessment (49) and may be a better predictor of cognitive performance.

Furthermore, in contrast to (prospective) studies on associations between BP variability and cardiovascular complications (50), we did not find clear associations of BP variability with cognitive functions. Although effects of BP variability on the heart may differ from effects on the brain, we may have failed to find associations because of the relatively young age of our sample and because the cross-sectional design did not allow us to examine effects of BP variability on cognitive change over time.

To the best of our knowledge, this is the first study to examine both linear and nonlinear (quadratic) associations between ABPM and multiple cognitive tests stratified by diabetes status. In one previous study (51), the (inverse) association between 24-h DBP and cognitive performance was stratified by diabetes status in a subanalysis (stratification did not seem to alter the relationship). However, this study was only performed in older men and lacked data on memory performance, and associations of nondipping with cognitive functions were not stratified by diabetes status. Another strength of our study is that we were able to adjust for a wide range of potential confounders.

Our study is not without limitations. Due to the cross-sectional design, we were unable to examine temporality of effects, let alone causal relationships. Although we used tests for cognitive domains that have been shown to be sensitive to effects of hypertension (52), it is possible that we missed subtle effects of BP on cognitive functions in the group without diabetes, which was healthier and younger. Such effects may become manifest in longitudinal data where participants show more advanced stages of cognitive aging (52). In addition, we did not have data on glucose levels at the time of the cognitive assessment. Therefore, we cannot exclude the possibility that cognitive test results in individuals with diabetes were influenced by relatively high or low glucose levels, although this should be considered part of the diabetic condition. Furthermore, we could not examine the potential confounding role of sleep apnea, which is more frequent in individuals with diabetes, in the associations of 24-h DBP with cognitive functions. Last, we did not have brain imaging data to examine potential mechanisms, e.g., cerebral small vessel disease, which may be involved in the association between DBP and cognitive decline.

In conclusion, this study shows that both low and high 24-h DBP are associated with poorer performance on tests for information processing speed and memory in individuals with type 2 diabetes, but not in those without diabetes. These results suggest that not only high BP but also low BP levels may increase the risk of cognitive impairment in individuals with type 2 diabetes, which may be important to consider in the therapeutic management of (diastolic) BP levels in those individuals. Monitoring of both BP levels and cognitive performance seems important in individuals with type 2 diabetes. Future (longitudinal) studies should focus on causality and underlying mechanisms.

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Author Contributions. F.R.J.V., S.J.S.S., A.K., P.C.D., R.M.A.H., N.C.S., C.J.H.v.d.K., M.T.S., and A.A.K. contributed to conception and design, revised the manuscript critically for important intellectual content, and provided final approval of the version to be published. P.J.J.S. contributed to conception and design, participated in acquisition of data, analyzed and interpreted data, drafted the manuscript, revised the manuscript critically for important intellectual content, and provided final approval of the version to be published. M.P.J.v.B., S.K., and C.D.A.S. contributed to conception and design, contributed to analyses and interpretation of data, revised the manuscript critically for important intellectual content, and provided final approval of the version to be published. P.J.J.S. 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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