



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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Peggy J.J. Spauwen,^{1,2}
 Martin P.J. van Boxtel,^{1,2}
 Frans R.J. Verhey,^{1,2} Sebastian Köhler,^{1,2}
 Simone J.S. Sep,^{3,4} Annemarie Koster,^{5,6}
 Pieter C. Dagnelie,^{4,6,7}
 Ronald M.A. Henry,^{3,4}
 Nicolaas C. Schaper,^{3,4}
 Carla J.H. van der Kallen,^{3,4}
 Miranda T. Schram,^{3,4}
 Abraham A. Kroon,^{3,4} and
 Coen D.A. Stehouwer^{3,4}

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),

¹Department of Psychiatry and Neuropsychology, Maastricht University Medical Centre, Maastricht, the Netherlands

²School for Mental Health and Neuroscience, Maastricht University, Maastricht, the Netherlands

³Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands

⁴Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, the Netherlands

⁵Department of Social Medicine, Maastricht University, Maastricht, the Netherlands

⁶School for Public Health and Primary Care, Maastricht University, Maastricht, the Netherlands

⁷Department of Epidemiology, Maastricht University, Maastricht, the Netherlands

Corresponding author: Martin P.J. van Boxtel, martin.vanboxtel@maastrichtuniversity.nl.

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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 ethical 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 $(0.412 \times 24\text{-h PP})$ (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 $\geq 20\%$ (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 ^a
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 ^b
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 (Volts), median (IQR) ^c	9.2 (6.3–13.5)	13.4 (9.8–20.8)	<0.001 ^b
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 ^b

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. ^aP for difference between groups. ^bP values are derived from independent samples Student *t* tests with log-transformed outcomes. ^cAvailable 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 + $1/3 * [24\text{-h SBP} - 24\text{-h DBP}]$) 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

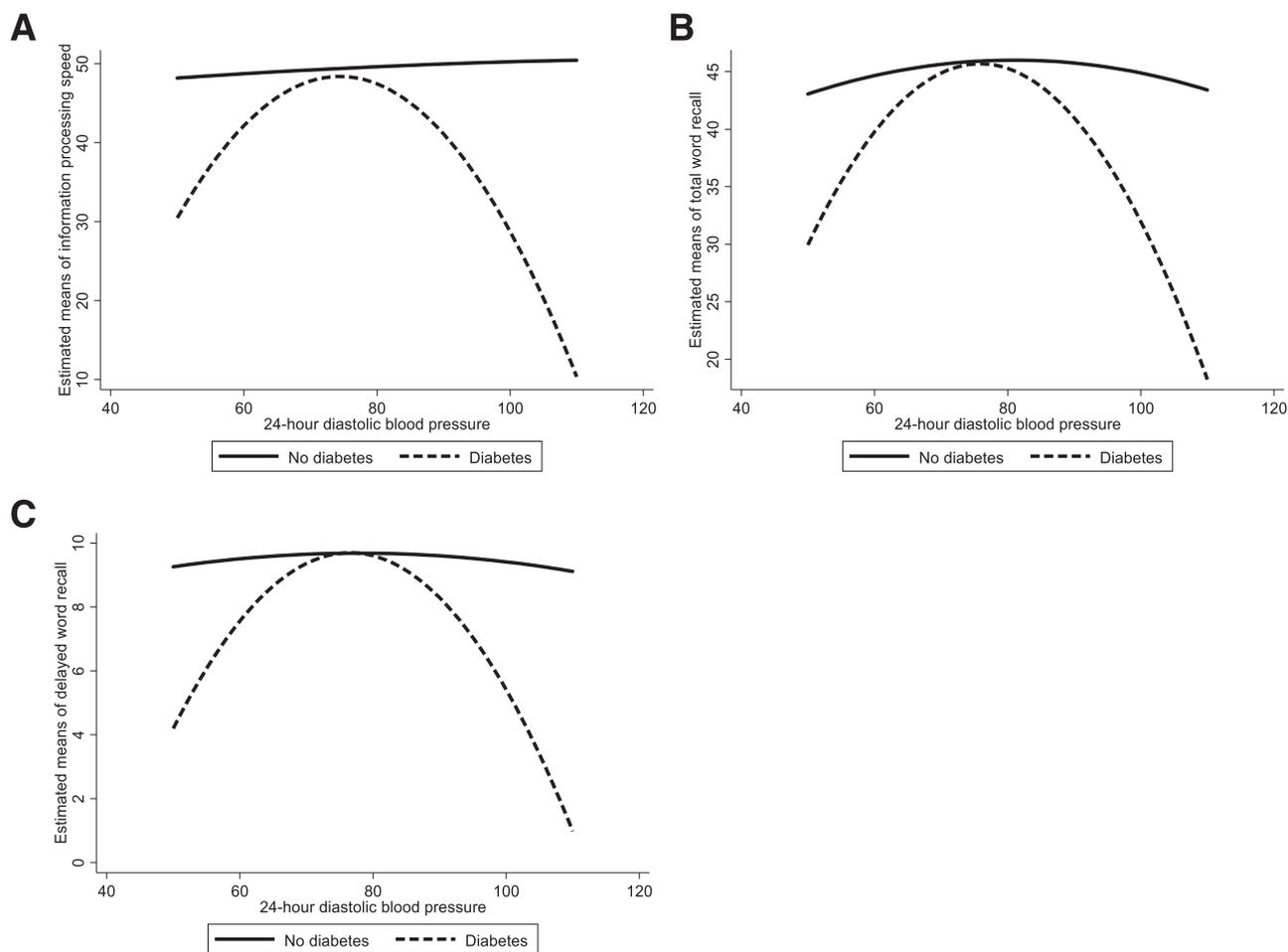


Figure 1—Interaction of nonlinear (quadratic) 24-h DBP (mmHg) and diabetes (solid, no diabetes; dash, diabetes) for information processing speed (number of digits) (A), immediate word recall (number of words) (B), and delayed word recall (number of words) (C).

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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References

1. Spauwen PJ, Köhler S, Verhey FR, Stehouwer CD, van Boxtel MP. Effects of type 2 diabetes on 12-year cognitive change: results from the Maastricht Aging Study. *Diabetes Care* 2013;36:1554–1561
2. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006;5:64–74
3. van den Berg E, Dekker JM, Nijpels G, et al. Blood pressure levels in pre-diabetic stages are associated with worse cognitive functioning in patients with type 2 diabetes. *Diabetes Metab Res Rev* 2009;25:657–664
4. Bruce DG, Davis WA, Casey GP, et al. Predictors of cognitive impairment and dementia in older people with diabetes. *Diabetologia* 2008;51:241–248
5. Hassing LB, Hofer SM, Nilsson SE, et al. Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study. *Age Ageing* 2004;33:355–361
6. Xu WL, Qiu CX, Wahlin A, Winblad B, Fratiglioni L. Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Neurology* 2004;63:1181–1186
7. Korf ES, van Straaten EC, de Leeuw FE, et al.; LADIS Study Group. Diabetes mellitus, hypertension and medial temporal lobe atrophy: the LADIS study. *Diabet Med* 2007;24:166–171
8. Gregg EW, Yaffe K, Cauley JA, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? Study

- of Osteoporotic Fractures Research Group. *Arch Intern Med* 2000;160:174–180
9. White WB, Wolfson L, Wakefield DB, et al. Average daily blood pressure, not office blood pressure, is associated with progression of cerebrovascular disease and cognitive decline in older people. *Circulation* 2011;124:2312–2319
 10. Yano Y, Kario K. Nocturnal blood pressure, morning blood pressure surge, and cerebrovascular events. *Curr Hypertens Rep* 2012;14:219–227
 11. van Boxtel MP, Gaillard C, Houx PJ, Buntinx F, de Leeuw PW, Jolles J. Is nondipping in 24 h ambulatory blood pressure related to cognitive dysfunction? *J Hypertens* 1998;16:1425–1432
 12. Okuno J, Yanagi H. Cognitive impairment and nocturnal blood pressure fall in treated elderly hypertensives. *Environ Health Prev Med* 2003;8:124–132
 13. Ayala DE, Moyá A, Crespo JJ, et al.; Hygia Project Investigators. Circadian pattern of ambulatory blood pressure in hypertensive patients with and without type 2 diabetes. *Chronobiol Int* 2013;30:99–115
 14. Waldstein SR, Giggey PP, Thayer JF, Zonderman AB. Nonlinear relations of blood pressure to cognitive function: the Baltimore Longitudinal Study of Aging. *Hypertension* 2005;45:374–379
 15. Taylor C, Tillin T, Chaturvedi N, et al. Midlife hypertensive status and cognitive function 20 years later: the Southall and Brent revisited study. *J Am Geriatr Soc* 2013;61:1489–1498
 16. Schram MT, Sep SJ, van der Kallen CJ, et al. The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. *Eur J Epidemiol* 2014;29:439–451
 17. World Health Organization. *Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia*. Geneva, World Health Org., 2006
 18. O'Brien E, Coats A, Owens P, et al. Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British hypertension society. *BMJ* 2000;320:1128–1134
 19. Muris DM, Houben AJ, Kroon AA, et al. Age, waist circumference, and blood pressure are associated with skin microvascular flow motion: the Maastricht Study. *J Hypertens* 2014;32:2439–2449; discussion 2449
 20. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;34:2159–2219
 21. Meaney E, Alva F, Moguel R, Meaney A, Alva J, Webel R. Formula and nomogram for the sphygmomanometric calculation of the mean arterial pressure. *Heart* 2000;84:64
 22. Kario K, Shimada K, Pickering TG. Abnormal nocturnal blood pressure falls in elderly hypertension: clinical significance and determinants. *J Cardiovasc Pharmacol* 2003;41(Suppl. 1):S61–S66
 23. Folstein MF, Folstein SE, McHugh PR. "Minimal state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198
 24. Van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J. Rey's verbal learning test: normative data for 1855 healthy participants aged 24–81 years and the influence of age, sex, education, and mode of presentation. *J Int Neuropsychol Soc* 2005;11:290–302
 25. Stroop JR. Studies of interference in serial verbal reaction. *J Exp Psychol* 1935;18:643–662
 26. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. The Stroop color-word test: influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment* 2006;13:62–79
 27. van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J. The Letter Digit Substitution Test: normative data for 1,858 healthy participants aged 24–81 from the Maastricht Aging Study (MAAS): influence of age, education, and sex. *J Clin Exp Neuropsychol* 2006;28:998–1009
 28. Spauwen PJ, van Eupen MG, Köhler S, et al. Associations of advanced glycation end-products with cognitive functions in individuals with and without type 2 diabetes: the Maastricht study. *J Clin Endocrinol Metab* 2015;100:951–960
 29. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–612
 30. De Bie SE. *Standard Questions 1987: Proposal for Uniformization of Questions Regarding Background Variables and Interviews*. Leiden, the Netherlands, Leiden University Press, 1987 [in Dutch]
 31. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59 (Suppl. 20):22–33; quiz 34–57
 32. Bilo G, Giglio A, Styczkiewicz K, et al. A new method for assessing 24-h blood pressure variability after excluding the contribution of nocturnal blood pressure fall. *J Hypertens* 2007;25:2058–2066
 33. den Heijer T, Launer LJ, Prins ND, et al. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology* 2005;64:263–267
 34. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. *Diabetologia* 2008;51:527–539
 35. Witteman JC, Grobbee DE, Valkenburg HA, et al. J-shaped relation between change in diastolic blood pressure and progression of aortic atherosclerosis. *Lancet* 1994;343:504–507
 36. Creager MA, Lüscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Circulation* 2003;108:1527–1532
 37. Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev* 1959;39:183–238
 38. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990;2:161–192
 39. Kim YS, Immink RV, Stok WJ, Karemaker JM, Secher NH, van Lieshout JJ. Dynamic cerebral autoregulatory capacity is affected early in type 2 diabetes. *Clin Sci (Lond)* 2008;115:255–262
 40. Marthol H, Brown CM, Zikeli U, et al. Altered cerebral regulation in type 2 diabetic patients with cardiac autonomic neuropathy. *Diabetologia* 2006;49:2481–2487
 41. Cipolla MJ. Control of cerebral blood flow. In *Cerebral Circulation*. San Rafael, CA, Morgan & Claypool Life Science, 2009
 42. Low PA, Benrud-Larson LM, Sletten DM, et al. Autonomic symptoms and diabetic neuropathy: a population-based study. *Diabetes Care* 2004;27:2942–2947
 43. Mehrabian S, Duron E, Labouree F, et al. Relationship between orthostatic hypotension and cognitive impairment in the elderly. *J Neurol Sci* 2010;299:45–48
 44. Umegaki H, Iimuro S, Shinozaki T, et al.; Japanese Elderly Diabetes Intervention Trial Study Group. Risk factors associated with cognitive decline in the elderly with type 2 diabetes: pooled logistic analysis of a 6-year observation in the Japanese Elderly Diabetes Intervention Trial. *Geriatr Gerontol Int* 2012;12(Suppl. 1):110–116
 45. Akisaki T, Sakurai T, Takata T, et al. Cognitive dysfunction associates with white matter hyperintensities and subcortical atrophy on magnetic resonance imaging of the elderly diabetes mellitus Japanese elderly diabetes intervention trial (J-EDIT). *Diabetes Metab Res Rev* 2006;22:376–384
 46. Schmidt R, Schmidt H, Kapeller P, Lechner A, Fazekas F. Evolution of white matter lesions. *Cerebrovasc Dis* 2002;13(Suppl. 2):16–20
 47. van Boxtel MP, Henskens LH, Kroon AA, et al. Ambulatory blood pressure, asymptomatic cerebrovascular damage and cognitive function in essential hypertension. *J Hum Hypertens* 2006;20:5–13
 48. Sierra C, de La Sierra A, Mercader J, Gómez-Angelats E, Urbano-Márquez A, Coca A. Silent cerebral white matter lesions in middle-aged essential hypertensive patients. *J Hypertens* 2002;20:519–524
 49. Cuspidi C, Macca G, Michev I, et al. Short-term reproducibility of nocturnal non-dipping pattern in recently diagnosed essential hypertensives. *Blood Press* 2002;11:79–83
 50. Parati G, Ochoa JE, Salvi P, Lombardi C, Bilo G. Prognostic value of blood pressure variability and average blood pressure levels in patients with hypertension and diabetes. *Diabetes Care* 2013;36(Suppl. 2):S312–S324
 51. Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. *Hypertension* 1998;31:780–786
 52. Köhler S, Baars MA, Spauwen P, Schievink S, Verhey FR, van Boxtel MJ. Temporal evolution of cognitive changes in incident hypertension: prospective cohort study across the adult age span. *Hypertension* 2014;63:245–251