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# Carotid stiffness is associated with impairment of cognitive performance in individuals with and without type 2 diabetes. The Maastricht Study

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ABSTRACT

*Background and aims:* There is increasing evidence linking arterial (mainly aortic) stiffness and type 2 diabetes, a risk factor for arterial stiffness, to cognitive impairment and dementia. However, data on carotid stiffness, which may be especially relevant for cognitive performance, are scarce, and few studies have addressed the interplay between arterial stiffness, type 2 diabetes, and cognitive performance.
*Methods:* We studied individuals with (n = 197) and without (n = 528) type 2 diabetes, who completed a neuropsychological test battery and underwent applanation tonometry and vascular ultrasound to evaluate aortic (i.e. carotid-to-femoral pulse wave velocity) and carotid stiffness (i.e. distensibility, compliance and Young's elastic modulus). Linear regression analyses were performed and adjusted for demographics, vascular risk factors, and depression.
*Results:* Overall, our results showed that carotid, but not aortic, stiffness was associated with worse cognitive performance, primarily in the domains of processing speed (standardized regression coefficient for distensibility −0.083, $p = 0.040$; compliance −0.077, $p = 0.032$) and executive function and attention (distensibility −0.133, $p = 0.001$; compliance −0.090, $p = 0.015$; Young's elastic modulus −0.081, $p = 0.027$). These associations did not differ by diabetes status. The differences in cognitive performance between individuals with and without type 2 diabetes (mean difference in domain scores relative to those without diabetes for free recall memory −0.23, processing speed −0.19, executive function and attention −0.23; all $p \leq 0.009$ and adjusted for demographics, traditional vascular risk factors, and depression) were not substantially altered after additional adjustment for carotid stiffness.
*Conclusions:* Our findings suggest that carotid stiffness is associated with cognitive performance in both individuals with and without diabetes, but does not mediate the relationship between type 2 diabetes and cognitive dysfunction.


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## 1. Introduction

In the ageing population, a rapidly increasing number of individuals will face cognitive deterioration later in life. It is estimated that in the United States, 36% of individuals aged over 70 are affected by some form of cognitive impairment [1]. Yet, the pathophysiological mechanisms underlying age-related cognitive decline remain incompletely understood. Vascular factors are likely to be involved [2] and may not be limited to local abnormalities of the cerebral vasculature, but may also include systemic vascular alterations such as arterial stiffening.

Arterial stiffening is part of the normal ageing process and results from a complex interplay between structural and cellular changes within the arterial wall [3]. These changes include degenerative alterations, such as collagen accumulation, elastin fragmentation, and endothelial dysfunction [3]. In theory, stiffening of (central) elastic arteries will hamper the natural cushioning function of the arterial system, thereby increasing pulsatility of pressure and flow in the brain vasculature. This increased pulsatile load can cause microvascular damage [4,5] and may ultimately affect brain function.

Over the last decade, studies have collectively provided some evidence that arterial stiffness is negatively, but weakly, associated with cognitive performance [6]. So far, the main focus has been on carotid-to-femoral pulse wave velocity (cfPWV), a measure of aortic stiffness that is considered the gold standard for the assessment of arterial stiffness [7]. cfPWV, however, reflects stiffness of an arterial segment with mixed elastic and muscular properties [7], while stiffening of elastic and muscular arteries may differentially affect brain function, as the cushioning function of arteries diminishes from the most elastic to the more muscular ones [7]. To date, studies evaluating the association of local stiffness of the predominantly elastic common carotid artery with cognitive performance are scarce and have yielded conflicting results [8,9]. Moreover, few studies have explored the interplay between arterial stiffness, cognitive performance, and type 2 diabetes. Type 2 diabetes is known to be associated with a variety of cognitive problems [10], ranging from subtle cognitive decrements to overt dementia, and a growing body of evidence also suggests [11,12] that diabetes accelerates arterial stiffening. In addition, the ability of cerebral arteries to withstand increased pressure pulsatility may be decreased in individuals with diabetes [5]. As such, it can be hypothesized that arterial stiffness is involved in diabetes-associated cognitive problems, a hypothesis that is corroborated by data linking arterial stiffness to other microvascular complications of type 2 diabetes (e.g. nephropathy [13] and retinopathy [14]).

In view of the above, the aim of the present study was twofold. First, we investigated whether arterial stiffness was associated with cognitive performance in individuals with and without type 2 diabetes, and whether any such associations differed between aortic and carotid stiffness. Second, we investigated whether diabetes-associated impairment of cognitive performance could be explained by diabetes-associated increases in arterial stiffness, either aortic or carotid.

## 2. Materials and methods

### 2.1. Study population

In this study, we used data from The Maastricht Study, an ongoing observational prospective population-based cohort study that includes individuals aged 40–75 years living in the southern part of the Netherlands. The rationale and design have been described previously [15] and are summarised in the Online Supplement. For the present study, cross-sectional data from the first 866 participants were used who completed the baseline survey between November 2010 and March 2012. Participants with type 1 diabetes (n = 4) or possible dementia (i.e. those with a Mini Mental State Examination score <24, n = 3) were not eligible for the present study. From the eligible cohort, we additionally excluded a total of 134 (16%) individuals because of missing data on one or more of the following variables: cognitive performance (n = 20), cfPWV (n = 41; due to insufficient quality (n = 13) or logistical reasons (n = 28)), measures of local carotid stiffness (n = 62; due to technical failure (n = 5) or logistical reasons (n = 57)), or one or more covariates (n = 91). Therefore, 725 individuals were available for analysis of aortic stiffness, cognitive performance, and type 2 diabetes and 711 for analysis of indices of carotid stiffness, cognitive performance, and type 2 diabetes. Characteristics of individuals with complete and incomplete data are shown in Table S1 (Online Supplement).

The Maastricht 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.

### 2.2. Cognitive assessment

A concise battery (30 min) of neuropsychological tests was administered to assess cognitive performance [15]. For conceptual clarity, and to reduce the number of cognitive outcomes, test results were divided into three cognitive domains (i.e. free recall memory, processing speed, and executive function and attention), as specified in the Online Supplement. In short, free recall memory was evaluated using the Verbal Learning Test by averaging total immediate and delayed recall scores. The composite score for information processing speed was derived from the Stroop Colour Word Test Part I and II, the Concept Shifting Test Part A and B, and the Letter-Digit Substitution Test. Executive function and attention was assessed by the Stroop Colour Word Test Part III and the Concept Shifting Test Part C. Where necessary, individual test scores were inverted so that higher scores indicated better cognitive performance.

### 2.3. Diabetes status

A two-hour seven-sample oral glucose tolerance test was used to assess participants' glucose metabolism status, as previously described in more detail [15]. Based on the WHO 2006 diagnostic criteria [16], individuals were classified as having normal glucose metabolism, impaired glucose metabolism, or diabetes. Participants were also considered to have type 2 diabetes if they used glucose-lowering medication without a prior diagnosis of type 1 diabetes.

### 2.4. Measures of arterial stiffness

Details on the measures of arterial stiffness and their reproducibility are provided in the Online Supplement. During the vascular assessment, brachial systolic, diastolic, and mean arterial pressure (MAP) were determined repeatedly with a 5-min interval, using an oscillometric device (Accutorr Plus, Datascope Inc., Montvale, NJ, USA), and the average of these measurements was calculated.

### 2.5. Carotid-to-femoral pulse wave velocity

Carotid-to-femoral pulse wave velocity (cfPWV) was determined according to recent guidelines [17] with the use of

applanation tonometry (SphygmoCor, Atcor Medical, Sydney, Australia), as specified in the Online Supplement.

### 2.6. Indices of carotid stiffness

Elastic properties of the left common carotid artery (at least 10 mm proximal to the carotid bulb) were obtained by using an ultrasound scanner equipped with a 7.5-MHz linear probe (MyLab 70, Esaote Europe B.V., Maastricht, the Netherlands). This setup enabled the measurement of diameter (D), distension (ΔD) and intima-media thickness (IMT) as described elsewhere [18,19] and summarised in the Online Supplement. Combined with brachial pulse pressure (PP), these measures were used to calculate the following indices [20]:

- Carotid artery – Distensibility Coefficient (CarDC)

$$DC = (2\Delta D \cdot D + \Delta D^2)/(PP \cdot D^2)\ (10^{-3}\ kPa^{-1})$$

- Carotid artery – Compliance Coefficient (CarCC)

$$CC = \pi \cdot (2D \cdot \Delta D + \Delta D^2)/4PP\ (mm^2\ kPa^{-1})$$

- Carotid artery – Young's elastic modulus (CarYEM)

$$YEM = D/(IMT \cdot DC)\ (10^3\ kPa)$$

CarDC represents arterial stiffness, CarYEM the stiffness of the arterial wall material at operating pressure, and CarCC arterial buffering capacity. Please note that higher values of cfPWV and CarYEM, but lower values of CarDC and CarCC reflect greater arterial stiffness.

### 2.7. Covariates

A detailed description of the covariates is provided in the Online Supplement.

### 2.8. Statistical analyses

All analyses were performed using SPSS version 21.0 for Windows (IBM SPSS, IBM Corp, Armonk, NY, USA). Variables with a skewed distribution were transformed with the natural logarithm. A two-sided p-value <0.05 was considered statistically significant. No adjustments were made for multiple comparisons [21].

Multiple linear regression analyses were used to explore the association between measures of arterial stiffness, cognitive performance, and type 2 diabetes. The associations were adjusted for potential confounders, including demographic characteristics (i.e. age, sex, and educational level), haemodynamic factors (i.e. MAP and heart rate obtained during vascular assessment), cardiovascular risk factors (i.e. use of antihypertensive or lipid-modifying medication, total/high density lipoprotein-cholesterol ratio, triglyceride concentration, body mass index, smoking, alcohol consumption, and prior cardiovascular disease), and current depression where appropriate, as indicated in the tables. We deliberately chose to use slightly different models of adjustment across the different associations. Specifically, analyses with measures of arterial stiffness (e.g. the association between arterial stiffness and cognitive performance) were adjusted for mean arterial pressure to disentangle blood pressure-dependent and –independent effects of arterial stiffness on cognitive performance. For this purpose, mean arterial pressure was chosen as it provides information on the non-pulsatile component of blood pressure. The association between type 2 diabetes and cognitive performance, on the other hand, was adjusted for (office-based) systolic and diastolic blood pressure to enhance the comparability of findings with other studies. Multiplicative terms (e.g. CarDC * type 2 diabetes) were incorporated in the regression model to test interaction effects between type 2 diabetes and arterial stiffness on cognition with a confidence level of 90%. The assumptions of linear regression were verified prior to all analyses.

The mediation effects of arterial stiffness on diabetes-associated impairment of cognitive performance were assessed by calculating the changes in regression coefficients of type 2 diabetes after inclusion of arterial stiffness indices in the model. Corresponding 95% confidence intervals (CI) were estimated using SPSS macros provided by Preacher and Hayes [22] based on 5000 bootstrap iterations. A significant mediation effect was assumed when the 95% CI excluded zero. Mediation analyses were restricted to cognitive domains statistically significantly affected by the presence of diabetes and indices of arterial stiffness associated with cognitive performance.

Several sensitivity analyses were performed. First, analyses were repeated using indices of carotid stiffness that were calibrated with local carotid instead of brachial pulse pressure. Second, to examine the association between indices of carotid stiffness and cognitive performance in greater detail, we investigated whether the individual components of these indices (i.e. carotid diameter, distension, and pulse pressure) were associated with cognitive performance. We also evaluated the correlation between indices of carotid stiffness and carotid-to-femoral pulse wave velocity with use of the Pearson correlation coefficient. Third, we tested for the presence of an association between, on the one hand, central pulse pressure and the augmentation index, and, on the other, cognitive performance. Although central pulse pressure and the augmentation index, which were both determined by radial applanation tonometry (SphygmoCor, Atcor Medical, Sydney, Australia) and pulse wave analysis, are considered indirect measures of arterial stiffness, they may provide additional information on wave reflections [7]. Fourth, we evaluated the effect of adjustment for 24-h mean arterial pressure and heart rate instead of adjustment for the average mean arterial pressure and heart rate obtained during vascular assessment (24-h blood pressure data were only available in a subpopulation). Similarly, analysis of the association between type 2 diabetes and cognitive functioning were alternatively adjusted for mean arterial pressure, or for 24-h systolic and diastolic blood pressure [15], instead of office blood pressure. Fifth, we explored whether the association between type 2 diabetes and cognitive performance, or between type 2 diabetes and arterial stiffness, differed by hypertension status [15]. Lastly, the potential confounding effects of physical activity (self-reported hours of moderate to vigorous physical activity per week) were explored.

## 3. Results

Table 1 shows the characteristics of the study population (n = 725; mean age 60 ± 8 years) with (n = 197) and without (n = 528) diabetes. Overall, individuals with type 2 diabetes were older, more often male, and had a more adverse cardiovascular risk profile. They were also more likely to have a history of cardiovascular disease, except for stroke, and were, in general, less educated than individuals without diabetes. The prevalence of depression did not differ between the two groups.

Of the 528 individuals without diabetes, 124 (23%) were classified as having impaired glucose metabolism. Age- and sex-adjusted

**Table 1**
Characteristics of individuals with and without type 2 diabetes.

| Clinical characteristics | Total (n = 725) | Type 2 diabetes (n = 197) | No type 2 diabetes (n = 528) | *p*-value[a] |
|---|---|---|---|---|
| Age (years) | 60 ± 8 | 63 ± 7 | 58 ± 8 | <0.001 |
| Male | 396 (54.6%) | 137 (69.5%) | 259 (49.1%) | <0.001 |
| Educational level (low/middle/high) | 113/302/310 (15.6%/41.7%/42.8%) | 50/98/49 (25.4%/49.7%/24.9%) | 63/204/261 (11.9%/38.6%/49.4%) | <0.001 |
| BMI (kg/m$^2$) | 27.2 ± 4.4 | 29.6 ± 4.7 | 26.3 ± 4.0 | <0.001 |
| Total cholesterol (mmol/L) | 5.2 ± 1.2 | 4.4 ± 1.0 | 5.5 ± 1.1 | <0.001 |
| HDL-cholesterol (mmol/L) | 1.3 ± 0.4 | 1.1 ± 0.3 | 1.4 ± 0.4 | <0.001 |
| Total/HDL cholesterol ratio | 4.2 ± 1.2 | 4.2 ± 1.1 | 4.2 ± 1.3 | 0.678 |
| Triglycerides (mmol/L) | 1.2 [0.9–1.8] | 1.6 [1.1–2.3] | 1.1 [0.8–1.6] | <0.001 |
| Lipid-modifying medication | 255 (35.2%) | 150 (76.1%) | 105 (19.9%) | <0.001 |
| Brachial SBP (mmHg)[b] | 128 ± 14 | 132 ± 13 | 127 ± 14 | <0.001 |
| Brachial DBP (mmHg)[b] | 76 ± 7 | 76 ± 7 | 77 ± 8 | 0.385 |
| Brachial MAP (mmHg)[b] | 97 ± 10 | 99 ± 9 | 97 ± 10 | 0.025 |
| Brachial PP (mmHg)[b] | 52 ± 10 | 56 ± 11 | 50 ± 10 | <0.001 |
| Heart rate (bpm)[b] | 63 ± 9 | 66 ± 10 | 62 ± 8 | <0.001 |
| Hypertension[c] | 413 (57.0%) | 171 (86.8%) | 242 (45.8%) | <0.001 |
| Antihypertensive medication | 283 (39.0%) | 140 (71.1%) | 143 (27.1%) | <0.001 |
| eGFR (ml/min/1.73 m$^2$) | 89 ± 15 | 85 ± 16 | 90 ± 14 | <0.001 |
| Carotid-to-femoral pulse wave velocity (m/s) | 8.9 ± 2.1 | 9.8 ± 2.4 | 8.5 ± 1.8 | <0.001 |
| Alcohol consumption (no/low/high) | 120/381/224 (16.6%/52.6%/30.9%) | 53/103/41 (26.9%/52.3%/20.8%) | 67/278/183 (12.7%/52.7%/34.7%) | <0.001 |
| Smoking behaviour (never/former/current) | 226/384/115 (31.2%/53.0%/15.9%) | 45/123/29 (22.8%/62.4%/14.7%) | 181/261/86 (34.3%/49.4%/16.3%) | 0.004 |
| Prior cardiovascular disease | 125 (17.2%) | 56 (28.4%) | 69 (13.1%) | <0.001 |
| Current depression | 28 (3.9%) | 11 (5.6%) | 17 (3.2%) | 0.142 |
| | Total (n = 711) | Type 2 diabetes (n = 193) | No type 2 diabetes (n = 518) | *p*-value[a] |
| Carotid artery – distensibility coefficient ($10^{-3}$/kPa) | 13.7 ± 4.8 | 12.2 ± 4.1 | 14.2 ± 4.9 | <0.001 |
| Carotid artery – compliance coefficient (mm$^2$/kPa) | 0.65 ± 0.26 | 0.63 ± 0.24 | 0.66 ± 0.26 | 0.206 |
| Carotid artery – Young's elastic modulus ($10^3$/kPa) | 0.78 ± 0.36 | 0.86 ± 0.45 | 0.75 ± 0.31 | <0.001 |
| Carotid PP (mmHg)[d] | 51 ± 14 | 56 ± 15 | 49 ± 13 | <0.001 |

Data are presented as mean ± SD, median [IQR], or n (%).
BMI = Body Mass Index; HDL = high density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure; eGFR = estimated glomerular filtration rate.
[a] *p*-value for difference between individuals with and without type 2 diabetes, based on independent samples t-tests for continuous variables and Chi-square tests for categorical variables.
[b] Obtained from blood pressure measurements every 5 min during vascular assessment.
[c] Hypertension was defined as a systolic blood pressure ≥140 mmHg (based on office blood pressure measurements [15]), a diastolic blood pressure ≥ 90 mmHg, and/or current use of antihypertensive medication.
[d] N = 708, of which n = 191 with type 2 diabetes.

cognitive performance did not differ between individuals with normal and impaired glucose metabolism (data not shown). We therefore did not analyse these groups separately.

### 3.1. Arterial stiffness and cognitive performance

Table 2 shows the association between measures of arterial stiffness and cognitive performance. After adjustment for age, sex, and educational level, higher cfPWV tended to be associated with impaired free recall memory (standardized regression coefficient β [95% CI] −0.063 [−0.134 to 0.007], model 1) and information processing speed (−0.058 [−0.129 to 0.013], model 1), but these associations did not reach statistical significance. In the fully adjusted models (model 3), cfPWV was not associated with cognitive performance.

Lower carotid distensibility (CarDC) and compliance (CarCC) were associated with worse information processing speed and executive function and attention in fully adjusted models. Higher Young's elastic modulus (CarYEM) was only statistically significantly associated with lower performance in executive function and attention (β −0.081 [−0.152 to −0.009], model 3). Indices of carotid stiffness were not related to free recall memory (models 1–3). Calculations using the regression coefficients of age and indices of carotid stiffness (from the fully adjusted model, model 3) showed that one standard deviation increase in carotid stiffness was comparable with 1–2 years of ageing in the domain of processing speed and 2–4 years of ageing in the domain of executive function and attention (data not shown).

The associations between measures of arterial stiffness and cognitive functioning did not statistically significantly differ between individuals with and without diabetes (p-values for interaction ≥0.13).

### 3.2. Type 2 diabetes and cognitive performance

Table 3 shows the association between type 2 diabetes and cognitive performance. After adjustment for age, sex, and educational level, the presence of type 2 diabetes was associated with lower performance in all cognitive domains assessed (mean difference in cognitive domain scores for free recall memory [95% CI] −0.23 [−0.37 to −0.09]; processing speed −0.16 [−0.28 to −0.04]; executive function and attention −0.26 [−0.39 to −0.14]; model 1). Additional adjustments for multiple cardiovascular risk factors and current depression did not materially alter these associations (model 2). Raw cognitive test results for individuals with and without type 2 diabetes are presented in Table S2 (Online Supplement).

### 3.3. Type 2 diabetes and arterial stiffness

Table 4 shows the associations between type 2 diabetes and measures of arterial stiffness. After adjustment for age and sex, individuals with type 2 diabetes had higher cfPWV (mean

**Table 2**
Association between measures of arterial stiffness and cognitive performance.

| Model | Free recall Memory | Processing speed | Executive function & attention |
|---|---|---|---|
| **Carotid-to-femoral pulse wave velocity** | | | |
| Model 1 | −0.063 (−0.134 to 0.007) | −0.058 (−0.129 to 0.013) | 0.008 (−0.065 to 0.082) |
| Model 2 | −0.057 (−0.136 to 0.021) | −0.086[a] (−0.166 to −0.007) | 0.020 (−0.062 to 0.102) |
| Model 3 | −0.028 (−0.108 to 0.051) | −0.067 (−0.147 to 0.014) | 0.047 (−0.037 to 0.130) |
| **Carotid artery − distensibility coefficient** | | | |
| Model 1 | −0.032 (−0.104 to 0.040) | −0.060 (−0.133 to 0.012) | −0.125[a] (−0.200 to −0.051) |
| Model 2 | −0.022 (−0.101 to 0.057) | −0.087[a] (−0.166 to −0.008) | −0.143[a] (−0.224 to −0.061) |
| Model 3 | −0.007 (−0.085 to 0.071) | −0.083[a] (−0.162 to −0.004) | −0.133[a] (−0.215 to −0.052) |
| **Carotid artery − compliance coefficient** | | | |
| Model 1 | 0.003 (−0.065 to 0.071) | −0.061 (−0.130 to 0.007) | −0.088[a] (−0.159 to −0.018) |
| Model 2 | 0.012 (−0.058 to 0.082) | −0.073[a] (−0.144 to −0.003) | −0.091[a] (−0.164 to −0.018) |
| Model 3 | 0.007 (−0.063 to 0.076) | −0.077[a] (−0.147 to −0.007) | −0.090[a] (−0.163 to −0.018) |
| **Carotid artery − Young's elastic modulus ($10^3$/kPa)** | | | |
| Model 1 | −0.011 (−0.077 to 0.054) | −0.046 (−0.112 to 0.020) | −0.088[a] (−0.156 to −0.020) |
| Model 2 | −0.003 (−0.072 to 0.065) | −0.059 (−0.128 to 0.010) | −0.092[a] (−0.163 to −0.021) |
| Model 3 | 0.008 (−0.060 to 0.076) | −0.054 (−0.123 to 0.015) | −0.081[a] (−0.152 to −0.009) |

Data are presented as standardized regression coefficient (95% CI).
CI = confidence interval; SD = standard deviation.
[a] $p < 005$. Regression coefficients indicate the change in cognitive performance per SD increase in carotid-to-femoral pulse wave velocity or carotid Young's elastic modulus and per SD decrease in carotid distensibility or compliance; in other words, a negative regression coefficient means that greater arterial stiffness is associated with worse cognitive performance. **Model 1:** adjusted for age, sex, and educational level; **Model 2:** additional adjustments for mean arterial pressure and heart rate (the latter only for analyses of carotid-to-femoral pulse wave velocity); **Model 3:** additional adjustments for presence of type 2 diabetes, body mass index, total/high density lipoprotein-cholesterol ratio, triglycerides, use of lipid-modifying medication, use of antihypertensive medication, estimated glomerular filtration rate, smoking behaviour, alcohol consumption, current depression, history of cardiovascular disease(s).

**Table 3**
Mean difference in cognitive domain scores between individuals with and without type 2 diabetes.

| Model | Free recall memory | Processing speed | Executive function & attention |
|---|---|---|---|
| Model 1 | −0.229[a] (−0.371 to −0.088) | −0.160[a] (−0.278 to −0.042) | −0.260[a] (−0.385 to −0.136) |
| Model 2 | −0.230[a] (−0.397 to −0.064) | −0.187[a] (−0.327 to −0.047) | −0.231[a] (−0.380 to −0.081) |

Data are presented as unstandardized regression coefficient (95% CI).
CI = confidence interval.
[a] $p < 005$. Individuals without diabetes were used as the reference group. Regression coefficients indicate the mean difference in cognitive domain scores between individuals with and without type 2 diabetes. **Model 1:** adjusted for sex, age, and educational level; **Model 2:** additional adjustments for body mass index, total/high density lipoprotein-cholesterol ratio, triglycerides, lipid-modifying medication, systolic blood pressure, diastolic blood pressure, antihypertensive medication, estimated glomerular filtration rate, smoking behaviour, alcohol consumption, current depression, and history of cardiovascular disease(s).

difference [95% CI] 0.62 m/s [0.31 to 0.93]) and tended to have lower, albeit not statistically significant, CarDC (−0.71 $10^{-3}$/kPa [−1.44 to 0.02]) than individuals without diabetes (model 1). The association between diabetes status and cfPWV weakened, but remained significant after further adjustment for haemodynamic (0.49 m/s [0.21 to 0.77], model 2) and other cardiovascular risk factors (0.45 m/s [0.12 to 0.78], model 3), whereas the trend with CarDC was no longer observed in the fully adjusted model (−0.31 $10^{-3}$/kPa [−1.15 to 0.48], model 3). The age- and sex-adjusted differences in CarCC en CarYEM between individuals with and without type 2 diabetes were not statistically significant (model 1).

### *3.4. Mediation of the association between type 2 diabetes and cognitive performance by arterial stiffness*

The mediation analyses were restricted to the cognitive domains observed to be associated with indices of carotid stiffness: information processing speed and executive function and attention. Differences in cognitive performance between individuals with and without type 2 diabetes, adjusted for age, sex, and educational level, were only slightly diminished after additional adjustment for CarDC, CarCC, or CarYEM (maximum change in regression coefficient (i.e. change in mean differences in cognitive domain scores)

**Table 4**
Mean difference in indices of arterial stiffness between individuals with and without type 2 diabetes.

| Model | Carotid-to-femoral pulse wave velocity (m/s) | Carotid artery − distensibility coefficient ($10^{-3}$/kPa) | Carotid artery − compliance coefficient ($mm^2$/kPa) | Carotid artery − Young's elastic modulus ($10^3$/kPa) |
|---|---|---|---|---|
| Model 1 | 0.618[a] (0.309−0.927) | −0.710 (−1.437 to 0.018) | −0.017 (−0.059 to 0.024) | 0.046 (−0.013 to 0.106) |
| Model 2 | 0.490[a] (0.207−0.773) | −0.630 (−1.294 to 0.035) | −0.015 (−0.055 to 0.026) | 0.042 (−0.015 to 0.099) |
| Model 3 | 0.450[a] (0.117−0.783) | −0.309 (−1.149 to 0.479) | −0.033 (−0.080 to 0.015) | 0.018 (−0.049 to 0.086) |

Data are presented as unstandardized regression coefficient (95% CI).
CI = confidence interval.
[a] $p<005$. Individuals without diabetes were used as the reference group. Regression coefficients indicate the mean difference in indices of arterial stiffness between individuals with and without type 2 diabetes. **Model 1:** adjusted for sex and age; **Model 2:** additional adjustments for mean arterial pressure and heart rate (the latter only for analyses of carotid-to-femoral pulse wave velocity); **Model 3:** additional adjustments for body mass index, total/high density lipoprotein-cholesterol ratio, triglycerides, use of lipid-modifying medication, use of antihypertensive medication, smoking behaviour, estimated glomerular filtration rate, history of cardiovascular disease(s).

was −0.013, with a bootstrapped 95% CI of [−0.0384 to −0.0012]). In fully adjusted models there were no statistically significant mediation effects of carotid stiffness indices on the association of type 2 diabetes with cognitive performance (data not shown). Likewise, no mediation was found when exploring the combined mediating effects of aortic and carotid stiffness (e.g. cfPWV and CarDC, data not shown).

### 3.5. Sensitivity analyses

When carotid stiffness was calibrated with carotid instead of brachial pulse pressure (PP), the results were largely similar to those obtained with use of brachial PP (Tables S3 and S4, Online Supplement), except for the association between type 2 diabetes and carotid stiffness, which appeared slightly stronger (Table S3, Online Supplement). Specifically, after adjustment for demographics and haemodynamic factors, individuals with diabetes had a statistically significantly lower CarDC than those without (mean difference [95% CI] −1.04 [−1.94 to −0.15], model 1, and −0.94 [−1.71 to −0.16] $10^{-3}$/kPa, model 2, respectively), but this association was not independent of other traditional cardiovascular risk factors (−0.39 [−1.31 to 0.53] $10^{-3}$/kPa, model 3). Results of mediation analyses using indices of carotid stiffness that were calibrated with carotid PP were similar to those obtained with brachial PP (data not shown).

A more detailed analysis of the association between indices of carotid stiffness and cognitive performance showed that only carotid distension was statistically significantly associated with cognitive performance, whereas carotid diameter and PP, as well as brachial PP, were not (Table S5, Online Supplement). In addition, neither the augmentation index nor central PP appeared to be associated with cognitive performance (Table S6, Online Supplement). Mediation analyses performed in the fully adjusted models showed that none of these individual variables had any statistically significant mediating effect on the association between type 2 diabetes and cognitive performance, nor when they were combined with aortic stiffness (data not shown). Correlation analyses revealed that indices of carotid stiffness were only weakly to moderately correlated with cfPWV (Table S7, Online Supplement).

Associations between type 2 diabetes and cognitive performance, or between type 2 diabetes and arterial stiffness, may differ between individuals with and without hypertension. However, we found no such interaction, except for the association of diabetes with impairments in executive function and attention, which was present in individuals with hypertension (mean difference in cognitive domain score [95% CI] −0.27 [−0.45 to −0.10]), but not in individuals without hypertension (−0.06 [−0.39 to 0.27], fully adjusted models). Additional mediation analyses performed in the subgroup of individuals with hypertension showed that this association also was not mediated by carotid stiffness (data not shown).

Alternative adjustment for 24-h blood pressure and additional adjustment for physical activity did not materially alter our results (see Online Supplement).

## 4. Discussion

The results of this study show that greater carotid, but not aortic, arterial stiffness is associated with worse cognitive performance, both in individuals with and without type 2 diabetes. However, indices of carotid stiffness do not mediate the relationship between type 2 diabetes and worse cognitive performance.

Although interrelated, aortic and carotid stiffness are not interchangeable [23]. Aortic stiffness, as reflected by cfPWV, involves a segment of the arterial tree with both elastic and muscular properties [7], whereas the common carotid artery is a predominantly elastic vessel. Muscular arteries are characterized by a higher collagen to elastin ratio than elastic arteries [24]. Because the cushioning function progressively diminishes from the most elastic to the more muscular arteries [7], pulsatile load on the brain is particularly likely to increase with stiffening of elastic arteries [25]. As such, differences in structural properties may explain our finding that carotid, but not aortic, arterial stiffness was negatively associated with cognitive performance. This is further supported by our observation that stiffness of the femoral artery, an artery of the muscular type, was not associated with cognitive functioning (data not shown). Data from the ARIC (Atherosclerosis Risk In Communities) study have previously indicated that carotid stiffness is more strongly related to cerebrovascular disease (i.e. incident ischemic stroke) [26], whereas femoral stiffness has been suggested to be more strongly related to coronary heart disease [25].

To our knowledge, only three other studies have investigated the relationship between carotid stiffness and cognitive performance, with conflicting results. In line with our findings, findings of two studies in middle-aged (n = 58, mean age 53 ± 1 years) [9] and late middle-aged (n = 308, mean age 63 ± 6 years) [27] adults showed that carotid stiffness was associated with decrements in executive function and overall cognition [9,27], while cfPWV was not consistently associated with cognitive performance in these studies. In older individuals from the Rotterdam Study (n = 3714, mean age at baseline 72 ± 7 years), however, no association, neither cross-sectionally nor longitudinally, was observed between CarDC and (changes in) cognitive test scores after adjustment for cardiovascular risk factors [8]. Whether these differences in study results can be explained by differences in age is at present unknown. Aortic stiffness has been studied more frequently in relation to cognition. Our finding that cfPWV was not related to cognitive performance seems to be in contrast with most [4,8,9,28–41], but not all [42,43], previous studies. Part of this discrepancy may be explained by the fact that previous studies were often conduced in elderly subjects (i.e. mean age over 70) [4,8,28–33,39] or individuals with (subjective) memory loss [28–30,37], with larger between-individual variation in cognitive performance, and frequently did not control for potential confounders such as MAP [9,28–31,33,36,37] or depressive symptoms [8,9,28–30,36,37,39]. Nonetheless, this does not explain why our findings of cfPWV contrast with those of comparable population-based cohort studies [34,38,40,41], although this might be due to use of varying cognitive tests focusing on different aspects of cognitive performance. Given the current literature, we can thus not conclude from our data that aortic stiffness is unrelated to cognitive performance, but our data do suggest that carotid stiffness is more strongly associated with impairments in cognitive performance.

Although further studies are needed to fully elucidate the mechanisms that relate carotid stiffness to cognitive performance, it can be speculated that an impaired cushioning function of elastic arteries contributes to the development and progression of cerebral small-vessel disease. The potential role of the arterial cushioning function in linking carotid stiffness to cognitive performance is illustrated by our observation that carotid distension, but not carotid diameter or PP, was associated with cognitive performance. The consequential increase in pulsatile load on the brain is likely to induce alterations in the cerebral microcirculation (e.g. hypertrophic remodelling and rarefaction of small arteries) which, in turn, can lead to (chronic) cerebral ischaemia [44]. In this regard, our finding that neither PP nor the augmentation index was associated with cognitive performance may suggest that, as proposed previously [4], transmission of excessive flow rather than pressure

pulsatility has a negative impact on the cerebral microcirculation. It could, however, also reflect the fact that PP and the augmentation index are indirect measures of arterial stiffness that depend on multiple factors, including the duration and pattern of ventricular contraction [7].

The idea that cerebral small-vessel disease may link carotid stiffness to cognitive performance is supported by recent studies showing that carotid stiffness is associated with higher volumes of white matter hyperintensities [45,46] and non-lacunar infarcts [46], independently of other vascular factors. Carotid stiffness does, however, not predict the progression of cerebral small-vessel disease [46], which is inconsistent with small-vessel disease being an important factor contributing to the observed decrements in cognitive performance with carotid stiffness. Alternatively, carotid stiffness may affect carotid baroreceptor sensitivity [47] or could simply reflect structural changes in cerebral arteries including increased collagen deposition, calcification, and fibrosis.

It has been suggested that vascular factors [10], such as arterial stiffness, may also be involved in the pathogenesis of diabetes-associated cognitive problems. The profile and magnitude of diabetes-associated cognitive decrements in the present study are comparable with those reported in systematic reviews [48] and show that type 2 diabetes is associated with mild decrements in multiple cognitive domains. In this context, the observed interaction between diabetes and hypertension suggests that individuals with both conditions are at especially high risk of cognitive impairment, particularly in the domain of executive function and attention. Our finding that type 2 diabetes was more strongly associated with aortic than with carotid stiffness is consistent with the concept that diabetes may affect the stiffness of muscular arteries more strongly, or earlier, than of elastic arteries [12,49]. In addition, the overall good glycaemic control of individuals with diabetes in our cohort (HbA1c 6.9% [52 mmol/mol]) may have attenuated the association between diabetes and carotid stiffness in our cohort, because glycaemia and insulinaemia are major determinants of (carotid) arterial stiffness in diabetes [12,50–52]. Obviously, the weak associations observed between type 2 diabetes and carotid arterial stiffness made a mediation effect of carotid arterial stiffness on the relationship between type 2 diabetes and cognitive performance a priori unlikely. Therefore, we cannot exclude that such mediation effects exist in diabetic individuals with more severe carotid stiffening. In addition, our results do not preclude the possibility that other vascular factors, such as (carotid) atherosclerosis (i.e. large vessel pathology) or cerebral small vessel disease (i.e. small vessel pathology), rather than or in addition to metabolic variables, mediate the negative effects of type 2 diabetes on cognitive performance.

Strengths of this study include the evaluation of both aortic and local carotid arterial stiffness and the comprehensive set of demographic, haemodynamic and cardiovascular variables that could be taken into account in the analyses. Our study also had limitations. First, we used a complete case analysis approach, which may have resulted in underestimation of associations as individuals who were excluded were generally slightly less healthy (Table S1, Online Supplement). Notably, however, most of the missing data were unavailable due to logical or technical reasons. Data imputation was considered, but as The Maastricht Study is an ongoing study that aims to include 10,000 individuals, and the accuracy and validity of imputation is likely to increase with increasing sample size and increasing amount of data available, it was decided to wait until data collection is completed before missing values will be imputed. A second limitation is the fact that we were unable to capture all aspects of cognitive functioning, which may also have led us to underestimate the true association between arterial stiffness and cognitive performance. Third, we did not adjust for multiple testing, thereby increasing the possibility of false positive findings. We nonetheless believe that it is unlikely that the pattern we observed, and that was consistent across multiple sensitivity analyses, is solely explained by the play of chance. A fourth limitation concerns the accuracy of the calibration method used to determine local carotid PP. Specifically, we cannot exclude the possibility of a systematic error in our measurement of brachial MAP with resulting errors in the absolute values of carotid PP. Note, however, that such a systematic error would not affect the ranking of individuals, and hence is unlikely to have affected the outcome of the sensitivity analyses in which local carotid PP was used. Last, although we think that it is unlikely that (overall quite subtle) cognitive impairment leads to stiffening of the arteries, the cross-sectional nature of our study does not permit any conclusions on causality.

In conclusion, the present study shows that carotid arterial stiffness is associated with cognitive performance, but does not mediate the relationship between type 2 diabetes and cognitive dysfunction. Our findings indicate that stiffening of elastic and muscular arteries may differentially affect brain function, highlighting the importance of markers of carotid stiffness in studies linking arterial stiffening to brain function. Future (longitudinal) studies are warranted to confirm that our findings are not just a chance finding and may shed light on the mechanisms involved. Hypothetically, our results suggest that prevention and treatment of increased carotid stiffness could serve as new targets to preserve cognitive function, at least on a population level. The effectiveness of interventions targeting carotid stiffness on the individual level might be limited given the rather weak associations observed, which, however, does not preclude carotid stiffening from being a causative factor for cognitive deterioration and the development of dementia.

## Conflict of interest

GJB consults for and receives research support from Boehringer Ingelheim, consults for Takeda Pharmaceuticals, and has received speaker's fees from Eli Lilly. The other authors have no conflicts of interest to declare.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2016.07.912.

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