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# Carotid circumferential wall stress is not associated with cognitive performance among individuals in late middle age: The Maastricht Study

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ABSTRACT

*Background and aims:* Arterial remodelling aims at normalising circumferential wall stress (CWS). Greater CWS in the carotid artery has previously been associated with the prevalence and severity of cerebral small vessel disease, a major cause of ageing-related cognitive decline. Here we test the hypothesis that greater carotid CWS is associated with poorer cognitive performance.

*Methods:* We studied 722 individuals (60 ± 8 years, 55% men, 42.5% highly educated, blood pressure 137 ± 19/77 ± 11 mmHg, n = 197 with type 2 diabetes) who completed a neuropsychological assessment and underwent vascular ultrasound to measure the intima-media thickness (IMT) and interadventitial diameter (IAD) of the left common carotid artery at a plaque-free site. From IMT and IAD, lumen diameter (LD) was calculated. These structural measures were then combined with local carotid pulse pressure and brachial mean arterial pressure to obtain a measure of pulsatile ($CWS_{pulsatile}$) and average ($CWS_{mean}$) mechanical load on the vessel wall. Cognitive domains assessed were memory, executive function and attention, and processing speed.

*Results:* After adjustment for age, sex, and education, regression analyses showed that neither $CWS_{pulsatile}$ nor $CWS_{mean}$ were associated with measures of cognitive performance (p-values ≥0.31). This null association did not differ by age or educational level, and was observed in both individuals with and without carotid plaque, diabetes and/or hypertension. In addition, none of the individual measures of carotid structure (i.e. IMT, IAD, and LD) was related to cognitive performance.

*Conclusions:* The present cross-sectional study shows that carotid CWS is not associated with cognitive performance, at least not among relatively highly educated individuals in late middle age with adequately controlled cardiovascular risk factors.



## 1. Introduction

Cognitive impairment and dementia are among the most feared conditions of old age [1] and their prevalence, with the ageing of the population, continues to grow [2]. Despite intensive research efforts, the mechanisms underlying age-related deterioration in

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cognitive performance remain incompletely understood. Vascular factors play an important role [3] and may include structural alterations of the carotid arteries, the main suppliers of blood to the brain.

As the vasculature ages [4], but also in response to haemodynamic and atherosclerotic stimuli [5], carotid arteries undergo structural changes. This process of structural changes is known as arterial remodelling and is characterised by diameter widening and wall thickening [5–7], resulting from a complex interplay between vasoactive molecules, extracellular matrix turnover, and inflammatory activity [5,6]. It is thought that arterial remodelling aims at normalising circumferential wall stress (CWS) [5]. Arterial remodelling is, however, not a uniform process [5–7] and can be maladaptive, resulting in greater CWS, as is, for example, the case in diabetes [5].

In theory, there are at least two mechanisms through which carotid CWS might influence cognitive performance. First, greater CWS has been related to the risk of plaque fissuring [8] and rupture [9] with consequential (micro)embolisation of plaque debris to the brain. Cerebral emboli cause neuronal ischaemia, which can ultimately lead to neuronal dysfunction and cell death. Alternatively, or simultaneously, greater CWS may induce endothelial dysfunction [10], even in the absence of carotid plaque, which at the level of the downstream microcirculation can contribute to blood-brain barrier disruption. Such disruption has been suggested to precipitate cerebral small vessel disease (CSVD) [11]. Collectively, CWS may thus be linked to cognitive performance through vascular damage of the brain. Indeed, previous studies have shown that circumferential wall tension [12] and stress [13] are associated with a greater prevalence of silent lacunar infarcts [12] and a greater volume of white matter hyperintensities (WMH) [13]. To date, however, data on the association of CWS with cognitive performance are lacking. We therefore tested the hypothesis that greater carotid CWS is associated with impairments of cognitive performance.

## 2. Patients and methods

### 2.1. Study population

In this study, we used data from The Maastricht Study, an observational prospective population-based cohort study enriched with individuals with type 2 diabetes. The rationale and design have been described previously [14]. In brief, the study focuses on the aetiology, pathophysiology, complications, and comorbidities of type 2 diabetes and is characterised by an extensive phenotyping approach. All individuals aged between 40 and 75 years living in the southern part of the Netherlands and sufficiently proficient in the Dutch language were eligible for participation. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. For reasons of efficiency, recruitment was stratified according to known type 2 diabetes status.

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. Each participant underwent all examinations within a time window of three months. We excluded participants with type 1 diabetes (n = 4), as well as those with missing data (n = 140) on cognitive performance (n = 21), CWS (n = 53), and/or one or more of the potential confounders (n = 80). 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

All individuals completed a concise (30 min) neuropsychological test battery to assess cognitive performance [14]. For conceptual clarity and to increase the robustness of the underlying cognitive construct, test scores were standardized and divided into three cognitive domains (i.e. memory function, executive function and attention, and information processing speed), as detailed in the Supplementary Data (see Extended methods, Supplementary Data). In short, memory function 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. Circumferential wall stress

Carotid ultrasound examinations were performed by trained vascular technicians who were unaware of the participants' clinical characteristics. Measurements took place in a dark, quiet, and temperature-controlled room (21–23 °C) and were performed in supine position after a resting period of 10 min. Talking or sleeping was not allowed during the examination. Structural properties of the left carotid artery (at least 10 mm proximal to the carotid bulb) were determined with use of an ultrasound scanner equipped with a 7.5-MHz linear probe (MyLab 70, Esaote Europe, Maastricht, the Netherlands). This setup enabled the measurement of intima-media thickness (IMT) and interadventitial diameter (IAD), as described elsewhere [15,16] and detailed in the Supplementary Data.

Briefly, based on radio frequency multiple M-line analysis, mean IMT and IAD were calculated along a plaque-free segment of the left common carotid artery during end-diastole. IMT was defined as the distance between the lumen-intima and media-adventitia interfaces of the far (posterior) wall. IAD was defined as the distance between the media-adventitia interfaces of the near and far wall. The median IMT and IAD of three consecutive measurements were used in the analyses.

From IMT and IAD, lumen diameter (LD) was calculated using the following formula: LD = IAD-(2*IMT) in mm [5]. CWS was then calculated according to Laplace's law as P*(r/w), where P is transmural pressure, r is lumen radius and w is wall thickness. For the present study, both pulse pressure (PP) and mean arterial pressure (MAP) were used as representatives of transmural pressure in order to obtain a measure of pulsatile ($CWS_{pulsatile}$) and average ($CWS_{mean}$) mechanical load on the vessel wall. Local carotid PP was obtained from carotid pressure waveform calibration as specified in the Supplementary Data (see Extended methods, Supplementary Data). Brachial MAP was measured repeatedly during the vascular assessment at a 5-min interval with use of a commercially validated oscillometric device (Accutorr Plus, Datascope Inc., Montvale, NJ, USA), and the average of these measurements was taken. With PP and MAP as representatives of transmural pressure, $CWS_{pulsatile}$ and $CWS_{mean}$ were calculated as (PP*(LD/2))/IMT and (MAP*(LD/2))/IMT, respectively, and expressed in kPa.

Reproducibility was assessed in 12 individuals (6 men; 60.8 ± 6.8 years; 6 with type 2 diabetes) who were examined by two observers at two occasions spaced one week apart. The intra- and inter-observer intra-class correlation coefficients were, respectively, 0.90 and 0.91 for IMT, and 0.98 and 0.95 for IAD.

Although IMT and IAD were measured at a plaque-free site, the

presence (yes/no) of plaque was recorded. In line with the Mannheim consensus, carotid plaque was defined as a focal thickening encroaching into the carotid lumen of more than 1.5 mm (as measured from the intima-lumen interface to the media-adventitia interface) or at least 50% of the surrounding IMT. Plaque could be located at either side of the common carotid artery, internal carotid artery, or bulbus. Data on the degree of carotid stenosis was not available in the present study.

### 2.4. Covariates

As described in more detail elsewhere [14], diabetes status was ascertained by an oral glucose tolerance test in those not treated with insulin, and defined according to the 2006 WHO [17] diagnostic criteria. Participants were also considered to have type 2 diabetes if they were prescribed glucose-lowering medication without a prior diagnosis of type 1 diabetes. Information on alcohol consumption, smoking behaviour (never/former/current), and prior cardiovascular disease (CVD) was collected from web-based questionnaires [14]. Frequency of alcohol consumption was categorised as never, low (1–7 glasses per week for women, 1–14 glasses for men), or high (>7 glasses per week for women, >14 for men) [14]. Prior CVD was defined as a history of myocardial infarction, stroke, or vascular surgery (including angioplasty) of coronary, carotid, abdominal aortic, or peripheral arteries [14]. Hypertension was defined as a systolic blood pressure $\geq$140 mmHg (based on office blood pressure measurements [14]), a diastolic blood pressure $\geq$ 90 mmHg, and/or use of antihypertensive medication. Medication use was determined as described previously [14]. An automatic analyser (Beckman Synchron LX20, Beckman Coulter Inc., Brea, USA) was used to measure fasting serum concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and creatinine. Cystatin C was measured by a particle enhanced immunoturbidimetric assay (Roche Cobas 8000, Roche Diagnostics, Basel, Switzerland). Glomerular filtration rate (eGFR) was estimated from both serum creatinine and cystatin C concentrations using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [18]. Body Mass Index (BMI) was calculated as body mass (kg) divided by height (m) squared. Educational level was derived from self-report and classified as low (i.e. no education, primary education, or lower vocational education), intermediate (i.e. intermediate general secondary school, intermediate vocational education, or higher secondary education), or high (i.e. higher vocational education or university). The Mini International Neuropsychiatric Interview (MINI) was used to detect the presence of a current depression [14].

### 2.5. Statistical analyses

Multiple linear regression analyses were used to analyse the association between CWS and cognitive performance. First, the association between (tertiles of) CWS and cognitive performance was explored in the total study population. As detailed in the Supplementary Data, these associations were adjusted for demographic characteristics (i.e. age, sex, and educational level; model 1) and additionally for cardiovascular risk factors (i.e. BMI, total cholesterol/HDL ratio, triglyceride concentration, use of lipid-modifying medication, hypertension, type 2 diabetes, eGFR, smoking, alcohol consumption, and prior CVD; model 2) and the presence of a current depression (model 3). With use of a similar approach, the association between the individual components of CWS (i.e. IMT, IAD, PP and MAP) and cognitive performance was explored. We also evaluated whether the lumen-to-wall ratio, calculated as LD/(2*IMT), was associated with cognitive performance, as this measure provides information on the geometric aspects of CWS. Second, to investigate whether the association between CWS and cognitive performance differed by age, educational level, diabetes status, or the presence of hypertension or carotid plaque, we tested for the presence of multiplicative interaction by adding product terms to the regression models. Third, subgroup analysis were performed to explore the association between CWS and cognitive performance in individuals considered most prone for cognitive problems. To this end, we repeated the analyses after stratification for age (i.e. aged $\leq$60 or >60 years), educational level, diabetes status, the presence of carotid plaque, or the presence of hypertension. The cut-off for age was based on the concept that above the age of 60 the brain starts to undergo neurodegenerative changes [19]. We also performed a subgroup analysis in individuals with both type 2 diabetes and hypertension. Finally, we tested for the possibility of a non-linear association between CWS and cognitive performance by entering linear and quadratic terms of the mean-centered CWS to the initial regression models.

All statistical analyses were performed with use of SPSS for Windows, version 21.0 (IBM SPSS, IBM Corp, Armonk, NY, USA). Variables with a skewed distribution (i.e. $CWS_{pulsatile}$, Stroop Colour Word Test scores, Concept Shifting Test scores, and triglyceride concentrations) were transformed with the natural logarithm prior to analyses. A two-sided $p$-value < 0.05 was considered statistically significant, except for interaction analyses where the significance level was set at 0.10.

## 3. Results

Demographic and clinical characteristics of the 722 individuals available for analysis are shown in Table 1, stratified according to tertiles of $CWS_{pulsatile}$. Overall, participants were of late middle age (mean age 60 ± 8 years) and slightly more likely to be male (55.1%). Note that although in general the cardiovascular risk profile worsened with increasing CWS, cardiovascular risk factors were generally adequately controlled (Table 1). Characteristics of individuals excluded from the analyses due to incomplete data (n = 140; 16%) are presented in Table E1 (Supplementary Data). In brief, those excluded more often had type 2 diabetes and more frequently suffered from a current depression. In addition, they performed slightly worse on tests of memory function.

### 3.1. Circumferential wall stress and cognitive performance

Table 2 shows the association between tertiles of CWS and cognitive performance. After adjustment for age, sex, and educational level, cognitive performance did not differ statistically significant across tertiles of either $CWS_{pulsatile}$ or $CWS_{mean}$ (model 1). Additional adjustments for cardiovascular risk factors and current depression did not materially change these results (models 2 and 3). Similar null results were also obtained when $CWS_{pulsatile}$ and $CWS_{mean}$ were considered as continuous variables (all p-values $\geq$0.31, model 1; Table E2, Supplementary Data). When the individual components of CWS were evaluated, none of these (i.e. IMT, IAD, LD, PP, and MAP) was associated with performance on any of the cognitive domains examined (Table 3). Similarly, the lumen-to-wall ratio was unrelated to cognitive performance (Table 3).

Multiplicative interaction analyses indicated that the null association between CWS and cognitive performance did not differ by age ($p$-values for multiplicative interaction $\geq$0.15; model 1), educational level ($p \geq 0.11$), or the presence of hypertension ($\geq$0.29). In contrast, statistically significant interaction was observed between CWS and diabetes status for memory ($p$-values for interaction 0.04 ($CWS_{pulsatile}$) and 0.02 ($CWS_{mean}$)), as well as between CWS and the presence of carotid plaque for information

processing speed ($p$-value for interaction 0.03 ($CWS_{mean}$)).

Subsequent stratified analysis, however, revealed that there was no statistically significant association between CWS (i.e. $CWS_{pulsatile}$ and $CWS_{mean}$) and cognitive performance among individuals with or without type 2 diabetes (Table E3, Supplementary Data), nor among those with or without carotid plaque (n = 714; Table E4, Supplementary Data). Likewise, we did not observe any association between CWS and cognitive performance when subgroup analyses were performed in individuals aged ≤ and >60 (Table E5, Supplementary Data); individuals with different educational levels (Table E6, Supplementary Data), and individuals with and without hypertension (Table E7, Supplementary Data). CWS was also not associated with cognitive performance in individuals with both type 2 diabetes and hypertension (n = 170; Table E8, Supplementary Data). Finally, even in individuals with both type 2 diabetes and hypertension, of older age, and with a low educational level, no association was observed (n = 31; data not shown). Note that we did observe a statistically significant negative association between the presence of carotid plaque and executive function and attention (Table E9, Supplementary Data).

Apart from the presence of a linear association between CWS and cognitive performance, we also ruled out the presence of a non-linear (quadratic) association (Table E10, Supplementary Data).

In order to confirm that the null associations we observed between CWS and cognitive performance were unlikely to be explained by a lack of statistical power, we performed a post-hoc power analysis. With use of G*Power (available from https://www.gpower.hhu.de; $\alpha = 0.05$; $\beta = 0.80$), we calculated that the sample size used (n = 722) provided us the possibility to detect effect sizes (Cohen's f2) of below 0.02.

## 4. Discussion

The present cross-sectional study shows that, in a population-based cohort of individuals in late middle age and enriched for type 2 diabetes, carotid CWS is not associated with cognitive performance. This null association was observed in both individuals with and without carotid plaque, with and without diabetes, with and without hypertension, and regardless of age and educational level. Collectively, our findings do not support our hypothesis that greater CWS negatively impacts cognitive performance.

To our knowledge, this is the first study to investigate the association between CWS and cognitive performance. Our negative findings should be viewed in the light of the limited available data on CWS in relation to structural brain damage, in which greater CWS has been associated with the prevalence and severity of CSVD [12,13]. This discrepancy may originate from the concept of cognitive reserve, which reflects the brain's ability to withstand neuropathology before performance is affected [20], despite the

**Table 1**
Demographic and clinical characteristics of the study population.

| | Total (n = 722) | Tertiles of $CWS_{pulsatile}$ Low (n = 240) | Middle (n = 241) | High (n = 241) | $p$-value for trend[a] |
|---|---|---|---|---|---|
| Age (years) | 60 ± 8 | 57 ± 8 | 60 ± 9 | 62 ± 8 | <0.001 |
| Male | 398 (55.1%) | 119 (49.6%) | 130 (53.9%) | 149 (61.8%) | 0.007 |
| Educational level (low/middle/high) | 117/298/307 (16.2%/41.3%/42.5%) | 28/92/120 (11.7%/38.3%/50.0%) | 42/93/106 (17.4%/38.6%/44.0%) | 47/113/81 (19.5%/46.9%/33.6%) | <0.001 |
| BMI ($kg/m^2$) | 27.2 ± 4.4 | 26.3 ± 4.6 | 27.1 ± 4.3 | 28.3 ± 4.1 | <0.001 |
| Total cholesterol (mmol/L) | 5.3 ± 1.2 | 5.4 ± 1.2 | 5.2 ± 1.1 | 5.1 ± 1.2 | 0.025 |
| HDL-cholesterol (mmol/L) | 1.3 ± 0.4 | 1.4 ± 0.5 | 1.3 ± 0.4 | 1.2 ± 0.3 | <0.001 |
| Total/HDL cholesterol ratio | 4.2 ± 1.2 | 4.1 ± 1.2 | 4.2 ± 1.3 | 4.3 ± 1.2 | 0.114 |
| Triglycerides (mmol/L) | 1.2 [0.9–1.8] | 1.2 [0.8–1.6] | 1.2 [0.8–1.7] | 1.3 [1.0–2.1] | <0.001 |
| Lipid-modifying medication | 254 (35.2%) | 66 (27.5%) | 79 (32.8%) | 109 (45.2%) | <0.001 |
| Systolic blood pressure (mmHg)[b] | 137 ± 19 | 127 ± 17 | 137 ± 17 | 146 ± 17 | <0.001 |
| Diastolic blood pressure (mmHg)[b] | 77 ± 11 | 74 ± 11 | 77 ± 10 | 79 ± 11 | <0.001 |
| Antihypertensive medication | 280 (38.8%) | 71 (29.6%) | 86 (35.7%) | 123 (51.0%) | <0.001 |
| Beta-blockers | 130 (18.0%) | 27 (11.3%) | 34 (14.1%) | 69 (28.6%) | <0.001 |
| Diuretics | 100 (13.9%) | 25 (10.4%) | 26 (10.8%) | 49 (20.3%) | 0.002 |
| Calcium antagonists | 58 (8.0%) | 10 (4.2%) | 14 (5.8%) | 34 (14.1%) | <0.001 |
| RAS inhibitors | 210 (29.1%) | 57 (23.8%) | 61 (25.3%) | 92 (38.2%) | <0.001 |
| Antiplatelet medication | 114 (15.8%) | 26 (10.8%) | 31 (12.9%) | 57 (23.7%) | <0.001 |
| Impaired glucose metabolism[c] | 121 (16.8%) | 30 (12.5%) | 43 (17.8%) | 48 (19.9%) | 0.030 |
| Type 2 diabetes[c] | 197 (27.3%) | 55 (22.9%) | 53 (22.0%) | 89 (36.9%) | <0.001 |
| Alcohol consumption (no/low/high) | 120/381/221 (16.6%/52.8%/30.6%) | 30/127/83 (12.5%/52.9%/34.6%) | 37/133/71 (15.4%/55.2%/29.5%) | 53/121/67 (22.0%/50.2%/27.8%) | 0.008 |
| Smoking behaviour (never/former/current) | 224/383/115 (31.0%/53.0%/15.9%) | 80/119/41 (33.3%/49.6% 17.1%) | 72/132/37 (29.9%/54.8%/15.4%) | 72/132/37 (29.9%/54.8%/15.4%) | 0.777 |
| Prior cardiovascular disease | 126 (17.5%) | 36 (15.0%) | 31 (12.9%) | 59 (24.5%) | 0.006 |
| Current depression | 28 (3.9%) | 11 (4.6%) | 9 (3.7%) | 8 (3.3%) | 0.473 |
| Carotid intima-media thickness (mm) | 0.85 ± 0.15 | 0.89 ± 0.16 | 0.85 ± 0.15 | 0.81 ± 0.13 | <0.001 |
| Carotid interadventitial diameter (mm) | 7.81 ± 0.84 | 7.55 ± 0.75 | 7.76 ± 0.80 | 8.11 ± 0.87 | <0.001 |
| Carotid lumen diameter (mm) | 6.11 ± 0.73 | 5.77 ± 0.58 | 6.07 ± 0.65 | 6.48 ± 0.76 | <0.001 |
| Carotid plaque[d] | 262 (36.7%) | 69 (29.2%) | 81 (33.9%) | 112 (46.9%) | <0.001 |
| $CWS_{pulsatile}$ (kPa) | 24 [19–29] | 18 [16–19] | 24 [22–25] | 32 [29–36] | |
| $CWS_{mean}$ (kPa) | 48 ± 11 | 40 ± 7 | 47 ± 7 | 56 ± 11 | |

Data are presented as mean ± SD, median [IQR], or n (%).
BMI = body mass index; CWS = circumferential wall stress; RAS = renin-angiotensin system.
[a] $p$-value for trend as determined with use of one-way ANOVA for continuous variables and chi-square tests for categorical variables.
[b] Obtained from office blood pressure measurements.
[c] Based on the results of an oral glucose tolerance test and prescribed medication, as detailed elsewhere [14].
[d] Data available for n = 714.

**Table 2**
Associations between tertiles of circumferential wall stress and cognitive performance.

| | Memory | Processing speed | Executive function & attention |
|---|---|---|---|
| **$CWS_{pulsatile}$** medium *vs.* low | | | |
| Model 1 | −0.073 | −0.080 | 0.041 |
| | (-0.227; 0.081) | (-0.233; 0.073) | (-0.119; 0.200) |
| Model 2 | −0.103 | −0.115 | 0.030 |
| | (-0.255; 0.049) | (-0.268; 0.038) | (-0.130; 0.191) |
| Model 3 | −0.104 | −0.118 | 0.029 |
| | (-0.256; 0.048) | (-0.271; 0.035) | (-0.131; 0.190) |
| **$CWS_{pulsatile}$** high *vs.* medium | | | |
| Model 1 | 0.063 | 0.037 | −0.095 |
| | (-0.091; 0.217) | (-0.116; 0.190) | (-0.254; 0.065) |
| Model 2 | 0.116 | 0.065 | −0.043 |
| | (-0.038; 0.270) | (-0.090; 0.221) | (-0.205; 0.120) |
| Model 3 | 0.115 | 0.063 | −0.043 |
| | (-0.039; 0.269) | (-0.092; 0.218) | (-0.206; 0.119) |
| **$CWS_{pulsatile}$** high *vs.* low | | | |
| Model 1 | −0.011 | −0.043 | −0.054 |
| | (-0.168; 0.147) | (-0.200; 0.114) | (-0.218; 0.109) |
| Model 2 | 0.013 | −0.049 | −0.012 |
| | (-0.147; 0.174) | (-0.212; 0.113) | (-0.182; 0.157) |
| Model 3 | 0.012 | −0.055 | −0.014 |
| | (-0.149; 0.172) | (-0.216; 0.107) | (-0.184; 0.156) |
| **$CWS_{mean}$** medium *vs.* low | | | |
| Model 1 | 0.075 | −0.038 | −0.038 |
| | (-0.078; 0.227) | (-0.190; 0.114) | (-0.197; 0.120) |
| Model 2 | 0.059 | −0.068 | −0.043 |
| | (-0.093; 0.210) | (-0.220; 0.085) | (-0.203; 0.116) |
| Model 3 | 0.056 | −0.076 | −0.046 |
| | (-0.095; 0.208) | (-0.228; 0.076) | (-0.206; 0.113) |
| **$CWS_{mean}$** high vs. medium | | | |
| Model 1 | −0.049 | −0.009 | 0.001 |
| | (-0.205; 0.107) | (-0.164; 0.146) | (-0.161; 0.163) |
| Model 2 | −0.041 | −0.018 | −0.005 |
| | (-0.195; 0.113) | (-0.174; 0.137) | (-0.167; 0.157) |
| Model 3 | −0.039 | −0.013 | −0.003 |
| | (-0.194; 0.115) | (-0.168; 0.142) | (-0.166; 0.159) |
| **$CWS_{mean}$** high *vs.* low | | | |
| Model 1 | 0.026 | −0.047 | −0.037 |
| | (-0.130; 0.182) | (-0.203; 0.108) | (-0.200; 0.125) |
| Model 2 | 0.018 | −0.086 | −0.048 |
| | (-0.093; 0.210) | (-0.244; 0.072) | (-0.214; 0.117) |
| Model 3 | 0.017 | −0.089 | −0.049 |
| | (-0.140; 0.174) | (-0.247; 0.069) | (-0.215; 0.116) |

N = 722. Data are presented as standardized differences in cognitive performance between tertiles of pulsatile ($CWS_{pulsatile}$) and mean ($CWS_{mean}$) circumferential wall stress. $CWS_{pulsatile}$ was transformed with the natural logarithm prior to analysis. Model 1: adjusted for age, sex, and educational level; Model 2: additional adjustment for body mass index, total/high density lipoprotein-cholesterol ratio, triglycerides, use of lipid-modifying medication, hypertension, presence of type 2 diabetes, estimated glomerular filtration rate, smoking behaviour, alcohol consumption, and history of cardiovascular disease(s); Model 3: additional adjustment for the presence of a current depression.
CWS = circumferential wall stress.

fact that we did not observe any association between CWS and cognitive performance in subgroup analyses among older individuals, those with a lower educational level, those with carotid plaque, or those with a more pronounced adverse cardiovascular risk profile (i.e. those with diabetes, hypertension, or both). It is, in addition, important to note that previous studies have found CWS to be related to global WMH volume [13] but not deep subcortical WMH [12], while WMH in strategic white matter tracts are considered more relevant for cognitive performance than global WMH volume [21]. Likewise, single (silent) lacunar infarct at some, but not all, places may have a pronounced negative impact on cognitive performance [21]. This, combined with the relatively weak associations between CWS and CSVD reported in the previous studies [12,13], could explain our negative findings on cognition, which thus not necessarily contradict previous studies on the association of CWS with structural brain damage. At the same time, despite the fact that our post-hoc power calculation estimated that we had sufficient statistical power, we cannot fully exclude the possibility of a power problem as our study population had a modest sample size and consisted of individuals who were relatively well educated and had an adequately controlled cardiovascular risk profile. Note, however, that we used the same study population to show that markers of carotid stiffness are negatively associated with cognitive performance [22].

Carotid CWS and stiffness are closely interrelated because they are constructed from overlapping parameters. Hence, our negative findings on CWS seem to contrast with our previous findings on carotid stiffness [22]. Important in this regard is that our previous findings were mainly driven by reduced carotid distension. This suggests that functional changes of the carotid wall that hamper its cushioning function have a greater impact on cognitive performance than the structural changes that underlie carotid artery remodelling. From a conceptual point of view, this can be explained by the fact that reduced distensibility increases the pulsatile pressure and flow load on the brain, which in turn, causes cerebral microvascular damage, whereas CWS does not directly increase pressure or flow pulsatility. There is, however, also an alternative, methodological, explanation for the discrepancy between our current and previous findings. Recent research has suggested that CWS is more prone for measurement errors than most markers of arterial stiffness [23].

Previous studies on carotid artery structure and its associations with cognitive performance have focused only on one aspect of structure, namely IMT, which is often considered an early marker of atherosclerosis [24]. At first glance, our finding that IMT was not associated with any of the cognitive domains assessed seems to be in contrast with most, but not all [25–28], previous studies reporting that IMT is related to worse cognitive performance, accelerated cognitive decline, and an increased risk of dementia [29–48]. The majority of these studies [29–34,36–39,43,44,46,48] did, however, not specify whether IMT measurements were performed at a plaque-free site and may therefore have explored the cerebral effects of more severe stages of carotid atherosclerosis, especially when comparing highest to lowest quintiles of IMT [29,30,34]. In line with this suggestion, several studies included IMT measurements from the internal carotid artery [30–32,43,44,46,47] or carotid bifurcation [30,31,38,43,44,47], i.e. locations that are more prone to atherosclerosis [49]. Interestingly in this respect, a closer examination of data from the Framingham [46] and Tromsø [47] studies indicated that internal, but not common, carotid IMT is associated with cognitive dysfunction.

Our findings on IMT may imply that early stages of carotid atherosclerosis do not impact cognitive function, which seems plausible as mild abnormalities are unlikely to substantially alter cerebral haemodynamics. In addition, cerebral microemboli are considered to originate mainly from (unstable) carotid plaques and are more frequent with increasing severity of carotid stenosis [50]. It is also important to bear in mind that the IMT as measured in the present study, with a mean value of 0.85 mm, may in part reflect adaptive remodelling in response to haemodynamic changes rather than atherosclerosis per se. The concept that cognitive performance declines with the severity of carotid atherosclerosis is supported by our finding that the presence of carotid plaque was associated with worse performance on the domain of executive function and attention and further corroborated by studies [45,47] in which associations with cognition were stronger for the presence of carotid

**Table 3**
Associations of individual components of circumferential wall stress and the lumen-to-wall ratio with cognitive performance.

| Model | Memory | Processing speed | Executive function & attention |
|---|---|---|---|
| **Intima-media thickness** | | | |
| Model 1 | −0.028 (−0.095 to 0.039) | 0.041 (−0.026 to 0.108) | 0.017 (−0.053 to 0.086) |
| Model 2 | −0.017 (−0.083 to 0.049) | 0.048 (−0.019 to 0.114) | 0.030 (−0.040 to 0.099) |
| Model 3 | −0.016 (−0.082 to 0.051) | 0.052 (−0.014 to 0.119) | 0.032 (−0.038 to 0.101) |
| **Interadventitial diameter** | | | |
| Model 1 | −0.048 (−0.121 to 0.024) | 0.018 (−0.054 to 0.091) | −0.015 (−0.091 to 0.060) |
| Model 2 | −0.024 (-0.098 to 0.050) | 0.025 (-0.050 to 0.099) | −0.003 (-0.081 to 0.075) |
| Model 3 | −0.022 (-0.097 to 0.052) | 0.030 (-0.044 to 0.105) | −0.001 (-0.079 to 0.077) |
| **Lumen diameter** | | | |
| Model 1 | −0.041 (−0.112 to 0.031) | 0.001 (−0.070 to 0.072) | −0.025 (−0.099 to 0.049) |
| Model 2 | −0.018 (-0.091 to 0.055) | 0.004 (-0.070 to 0.077) | −0.018 (-0.095 to 0.058) |
| Model 3 | −0.017 (-0.090 to 0.056) | 0.007 (-0.066 to 0.081) | −0.017 (-0.094 to 0.060) |
| **Pulse pressure** *(carotid artery)* | | | |
| Model 1 | −0.009 (−0.077 to 0.059) | 0.011 (−0.057 to 0.079) | −0.026 (−0.097 to 0.044) |
| Model 2 | 0.006 (-0.065 to 0.076) | 0.017 (-0.054 to 0.088) | 0.001 (-0.074 to 0.075) |
| Model 3 | 0.006 (-0.064 to 0.076) | 0.018 (-0.053 to 0.089) | 0.001 (-0.073 to 0.075) |
| **Mean arterial pressure** *(brachial artery)* | | | |
| Model 1 | −0.011 (−0.075 to 0.053) | 0.029 (−0.034 to 0.093) | −0.019 (−0.085 to 0.047) |
| Model 2 | −0.027 (-0.096 to 0.042) | 0.009 (-0.061 to 0.078) | −0.015 (-0.087 to 0.058) |
| Model 3 | −0.026 (-0.095 to 0.043) | 0.012 (-0.057 to 0.081) | −0.014 (-0.087 to 0.059) |
| **Lumen-to-wall ratio** | | | |
| Model 1 | 0.009 (−0.056 to 0.074) | −0.031 (−0.096 to 0.034) | −0.021 (−0.088 to 0.047) |
| Model 2 | 0.012 (−0.052 to 0.076) | −0.036 (−0.101 to 0.029) | −0.028 (−0.096 to 0.040) |
| Model 3 | 0.011 (−0.053 to 0.076) | −0.038 (−0.103 to 0.026) | −0.029 (−0.097 to 0.039) |

N = 722. Data are presented as standardized regression coefficient (95% confidence interval), which reflect the change in cognitive performance per standard deviation increase in intima-media thickness, interadventitial diameter, lumen diameter, pulse pressure, mean arterial pressure, or lumen-to-wall ratio. Model 1: adjusted for age, sex, and educational level; Model 2: additional adjustment for body mass index, total/high density lipoprotein-cholesterol ratio, triglycerides, use of lipid-modifying medication, hypertension, presence of type 2 diabetes, estimated glomerular filtration rate, smoking behaviour, alcohol consumption, and history of cardiovascular disease(s); Model 3: additional adjustment for the presence of a current depression.

plaque than for carotid IMT. In line with this, data from the Framingham study indicated that severe stenosis (≥50%) is associated with poorer cognitive performance, whereas milder stenosis (≥25%) is not [46].

Our findings should be viewed in light of the following limitations. First, as partly discussed above, one might question the statistical power of our study and the generalisability of our findings because our study population consisted of late middle aged individuals with adequately controlled cardiovascular risk factors. Indeed, we cannot completely rule out the possibility of a power problem although this possibility seems unlikely given the post-hoc power calculation and sensitivity analyses performed. Note, in addition, that we used a population-based sample enriched with individuals with type 2 diabetes and did not select individuals based on the degree their cardiovascular risk factors were controlled. Hence, we believe our population represents a population that has access to quality medical care. The CWS observed in the present study was also largely comparable to that reported in other studies [13,51,52], which further confirms the generalisability of our findings. We nonetheless, similar to previous studies, measured CWS at a single moment in time while, undoubtedly, the duration of abnormalities in CWS might be relevant for its effects on brain structure and function. This is clearly a limitation of our cross-sectional approach. Last, for the present study, we were unable to include data on brain structure. Hence, we could not confirm or refute previous findings that CWS is associated with CSVD, which could have facilitated the interpretation of our findings. A notable strength of our study is the cognitive test battery used, which was constructed to assess cognitive performance across multiple domains and had the ability to detect even subtle impairments in cognitive performance.

In conclusion, our findings show that carotid CWS is unrelated to cognitive performance in cross-sectional analyses and thereby suggest that maladaptive carotid remodelling does not directly affect brain function, at least not in individuals in late middle age with presumably ample cognitive reserves and adequately controlled cardiovascular risk factors. As this is the first study to evaluate the association between CWS and cognitive performance, further and particularly larger, longitudinal research is clearly needed to verify our findings and their generalisability. Ideally, future studies should include simultaneously assessed measures of both cognitive performance and vascular brain pathology in order to identify potential differential effects of greater CWS on brain structure and function.

## Conflicts 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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## Author contributions

SLCG, SJSS, CDAS, and GJB were involved in study conception and design. SG participated in data acquisition and cleaning, analysed and interpreted the data, and prepared the manuscript. SJSS, CDAS, and GJB contributed to interpretation of the data and critically revised the manuscript for intellectual content. SSJS, CDAS, MTS, MPJvB, RMAH, KDR, NCS, PCD, and CJHvdK are responsible for data acquisition. MTS, MPJvB, RMAH, KDR, PCD, and CJHvdK also critically reviewed the manuscript for intellectual content. TTvS and JohR were involved in data acquisition and helped with the interpretation of the carotid ultrasound data. All authors approved the final version of this manuscript. SG 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.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.07.003.

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