

# Associations of Arterial Stiffness With Cognitive Performance, and the Role of Microvascular Dysfunction

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## Associations of Arterial Stiffness With Cognitive Performance, and the Role of Microvascular Dysfunction The Maastricht Study

Sytze P. Rensma, Coen D.A. Stehouwer, Martin P.J. Van Boxtel, Alfons J.H.M. Houben, Tos T.J.M. Berendschot, Jaap F.A. Jansen, Casper G. Schalkwijk, Frans R.J. Verhey, Abraham A. Kroon, Ronald M.A. Henry, Walter H. Backes, Pieter C. Dagnelie, Martin C.J.M. van Dongen, Simone J.P.M. Eussen, Hans Bosma, Sebastian Köhler, Koen D. Reesink, Miranda T. Schram, Thomas T. van Sloten

**Abstract**—The mechanisms underlying cognitive impairment are incompletely understood but may include arterial stiffness and microvascular dysfunction. In the population-based Maastricht Study, we investigated the association between arterial stiffness and cognitive performance, and whether any such association was mediated by microvascular dysfunction. We included cross-sectional data of 2544 participants (age, 59.7 years; 51.0% men; 26.0% type 2 diabetes mellitus). We used carotid-femoral pulse wave velocity and carotid distensibility coefficient as measures of aortic and carotid stiffness, respectively. We calculated a composite score of microvascular dysfunction based on magnetic resonance imaging features of cerebral small vessel disease, flicker light-induced retinal arteriolar and venular dilation response, albuminuria, and plasma biomarkers of microvascular dysfunction (sICAM-1 [soluble intercellular adhesion molecule-1], sVCAM-1 [soluble vascular adhesion molecule-1], sE-selectin [soluble E-selectin], and vWF [von Willebrand factor]). Cognitive domains assessed were memory, processing speed, and executive function. A cognitive function score was calculated as the average of these domains. Higher aortic stiffness (per m/s) was associated with lower cognitive function ( $\beta$ ,  $-0.018$  SD [95% CI,  $-0.036$  to  $-0.000$ ]) independent of age, sex, education, and cardiovascular risk factors, but higher carotid stiffness was not. Higher aortic stiffness (per m/s) was associated with a higher microvascular dysfunction score ( $\beta$ ,  $0.034$  SD [95% CI,  $0.014$  to  $0.053$ ]), and a higher microvascular dysfunction score (per SD) was associated with lower cognitive function ( $\beta$ ,  $-0.089$  SD [95% CI,  $-0.124$  to  $-0.053$ ]). Microvascular dysfunction significantly explained 16.2% of the total effect of aortic stiffness on cognitive function. The present study showed that aortic stiffness, but not carotid stiffness, is independently associated with worse cognitive performance, and that this association is in part explained by microvascular dysfunction. (*Hypertension*. 2020;75:1607-1614. DOI: 10.1161/HYPERTENSIONAHA.119.14307.) • [Data Supplement](#)

**Key Words:** albuminuria ■ biomarkers ■ magnetic resonance imaging ■ microcirculation ■ risk factors

Cognitive impairment and dementia have an enormous impact on patients and society, and their prevalence is rising. The mechanisms underlying cognitive impairment and dementia remain, however, incompletely understood, but may include arterial stiffness and microvascular dysfunction (MVD).<sup>1</sup>

Greater arterial stiffness leads to excessive arterial pressure and flow pulsatility, which may transmit distally and damage the cerebral microcirculation.<sup>1</sup> The cerebral microvasculature regulates many processes potentially affecting cognition, that is, cerebral perfusion, neurogenesis, neurovascular coupling,

blood-brain barrier permeability, and cerebral autoregulation.<sup>2</sup> Impairment of these processes may lead to neuronal dysfunction and ischemia, which may ultimately lead to lower cognitive performance.<sup>3</sup> In accordance, previous studies<sup>4-21</sup> have shown an association between greater arterial stiffness and worse cognitive performance and incident dementia. Most of these studies<sup>4-11,14-18,21</sup> focused on carotid-femoral pulse wave velocity (cfPWV), a measure of aortic stiffness, but only some<sup>12-17,19,20</sup> on carotid stiffness. In addition, MVD has been associated with cognitive decline and dementia.<sup>22</sup> However,

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whether any association between aortic or carotid stiffness and worse cognitive performance is explained, or mediated, by MVD remains largely unknown.

Microvascular function and structure can be measured noninvasively in various organs. These measures include magnetic resonance imaging (MRI) features of cerebral small vessel disease (CSVD), for example, lower total brain parenchyma volume, higher white matter hyperintensity volume, and presence of lacunar infarcts and cerebral microbleeds.<sup>23</sup> Previous studies have found an association between lower total brain parenchyma volume and presence and severity of cerebral small vessel disease,<sup>24,25</sup> and lower total brain parenchyma volume is, therefore, considered as an important measure of cerebral small vessel disease.<sup>23</sup> White matter hyperintensities and presence of lacunes and cerebral microbleeds are also thought to be closely related to cerebral microvascular dysfunction and damage.<sup>23</sup> Other measures are flicker light-induced retinal arteriolar and venular dilation response, which are also closely linked to the cerebral microvasculature, and, thus, may reflect its function<sup>26</sup>; albuminuria (urinary albumin excretion [UAE])<sup>27</sup>; and plasma biomarkers of MVD (eg, sICAM-1 [soluble intercellular adhesion molecule-1], sVCAM-1 [soluble vascular adhesion molecule-1], sE-selectin [soluble E-selectin], and vWF [von Willebrand factor]).<sup>28</sup> To the extent that MVD is a generalized phenomenon, UAE and plasma biomarkers of MVD may also reflect cerebral MVD.<sup>28</sup> Higher concentrations of these plasma biomarkers are thought to be derived mainly from the microcirculatory endothelium<sup>29</sup> and are associated with incident cardiovascular disease,<sup>30</sup> which makes it plausible that higher concentrations of these markers reflect greater microvascular endothelial dysfunction. These various measures of MVD (ie, CSVD features, retinal arteriolar and venular dilation response, UAE, and plasma biomarkers of MVD) can, therefore, be summarized into a MVD composite score. We previously showed that such a MVD composite score is associated with worse cognitive performance.<sup>2</sup>

In view of the above, the aims of the present study were to investigate the associations between aortic and carotid stiffness and cognitive performance, and to test whether any such associations are statistically mediated by a score of various MVD measures, including CSVD features, retinal arteriolar and venular dilation response, UAE, and plasma biomarkers of MVD.

## Materials and Methods

Data are available from The Maastricht Study for any researcher who meets the criteria for access to confidential data, and the corresponding author may be contacted to request data.

We used data from The Maastricht Study, an observational population-based cohort study. The rationale and methodology have been described previously.<sup>31</sup> In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of diabetes mellitus type 2 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, the municipal registries, and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known diabetes mellitus type 2 status, with an oversampling of individuals with diabetes mellitus type 2 for reasons of efficiency. The present report includes

cross-sectional data from 3451 participants who completed the baseline survey between November 2010 and September 2013. 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 Ministry of Health, Welfare, and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent.

For all measures, participants were asked to refrain from smoking and drinking caffeine-containing beverages 3 hours before the measurement. A light meal was allowed until  $\geq 90$  minutes before the examination.

## Arterial Stiffness

A more detailed description of the arterial stiffness measures is provided in Item S1 in the [Data Supplement](#) and has been described previously.<sup>17</sup> We determined cfPWV with the use of applanation tonometry (SphygmoCor, Atcor Medical, Sydney, Australia). We assessed local carotid arterial properties using an ultrasound scanner with a 7.5-MHz linear probe (MyLab 70, Esaote Europe B.V., Maastricht, the Netherlands). We quantified carotid stiffness by calculating the carotid distensibility coefficient (carDC). Carotid compliance coefficient and Young's elastic modulus were also determined.

## Measures of Microvascular Dysfunction

A detailed description all MVD measures is provided in Item S2, and has been described previously.<sup>2</sup> Brain MRI measurements were implemented from December 2013 onward and were available in 2313 of 3451 participants (67%). Brain MRI was performed on a 3T MRI scanner (Siemens Magnetom Prisma-fit Syngo MR D13D, Erlangen, Germany). We evaluated 4 CSVD features, that is, lower total brain parenchyma volume, higher white matter hyperintensity volume, and presence of lacunar infarcts and cerebral microbleeds. We measured retinal arteriolar and venular dilation response to flicker light exposure by the Dynamic Vessel Analyzer (Imedos, Jena, Germany). In addition, we assessed UAE in 24-hour urine samples and evaluated 4 plasma biomarkers of MVD, that is, sICAM-1, sVCAM-1, sE-selectin, and vWF.

## Cognitive Performance

We assessed cognitive performance using a concise neuropsychological test battery. A detailed description of the domain-specific cognitive function scores is provided in Item S4 and has been described previously.<sup>17</sup> For statistical efficiency, we constructed a cognitive function composite score as follows: we first standardized the test scores in the 3 cognitive domains memory, processing speed, and executive function, then averaged these standardized scores, and finally standardized this average. We evaluated memory with the Verbal Learning Test; processing speed with the Stroop Color-Word Test Part I and II, Concept Shifting Test Part A and B, and Letter-Digit Substitution Test; and executive function with the Stroop Color-Word Test Part III and Concept Shifting Test Part C.

## Statistical Analysis

We inverted (multiplying by  $-1$ ) total brain parenchyma volume, and the flicker light-induced retinal arteriolar and venular dilation responses so that higher values indicated worse microvascular function. White matter hyperintensity volume and UAE were log-transformed (base 2) to normalize their skewed distribution.

We summarized the 11 MVD measures (ie, 4 CSVD features, retinal arteriolar and venular dilation responses, UAE, and 4 plasma biomarkers of MVD) into a MVD score, as done previously.<sup>2</sup> The same weight was given to each individual MVD measure. We hypothesized that each MVD measure is associated with arterial stiffness and cognitive performance according to similar underlying mechanisms. The use of a composite score reduces the influence of the biological variability of its components and it reduces the chance of a type 1 error. The MVD score was calculated when at least data on one of the 11 MVD measures were available. The score was calculated as the standardized average of the individual standardized MVD measures. On

average, individuals included in the analysis had data available on 9 of the 11 measures, and 1178 individuals (46.3%) had data available on all 11 measures (Figure S1).

The statistical analysis proceeded in 2 stages. First, we used linear regression analysis to evaluate associations between cfPWV and carDC and the cognitive function composite score. We adjusted for the following potential confounders: age, sex, and education (model 1), additionally for glucose metabolism status, body mass index, smoking, alcohol use, total/high-density lipoprotein cholesterol ratio, and triglycerides (model 2) and then additionally for mean arterial pressure, heart rate, and use of antihypertensive and/or lipid-modifying medication (model 3). We additionally adjusted for prior cardiovascular disease, plasma biomarkers of low-grade inflammation, and current depression in a separate model (model 4). These factors were added in a separate model, because of the risk of overadjustment bias: these factors may be confounders but may also mediate the associations between arterial stiffness, microvascular dysfunction, and cognitive performance. A detailed description of the other covariates and the rationale for their inclusion in the models is provided in the Item S4. Second, we performed a formal mediation analysis to test the hypothesis that MVD explains the association between greater arterial stiffness and worse cognitive performance. The mediation model quantifies the degree to which a variable statistically explains the association between a determinant and an outcome variable. We used bootstrapping (10000 samples) to calculate bias-corrected 95% CIs of the explained associations using the PROCESS statistical package for PASW statistics.<sup>32</sup> The magnitude of the explained association was calculated as a percentage of the total association.

We tested interaction terms with age (continuous scale), sex, education, and glucose metabolism status to evaluate whether the association between arterial stiffness and cognitive performance differed according to these factors.

We did several additional predefined and post hoc analyses as detailed in the Item S5 in the [Data Supplement](#).

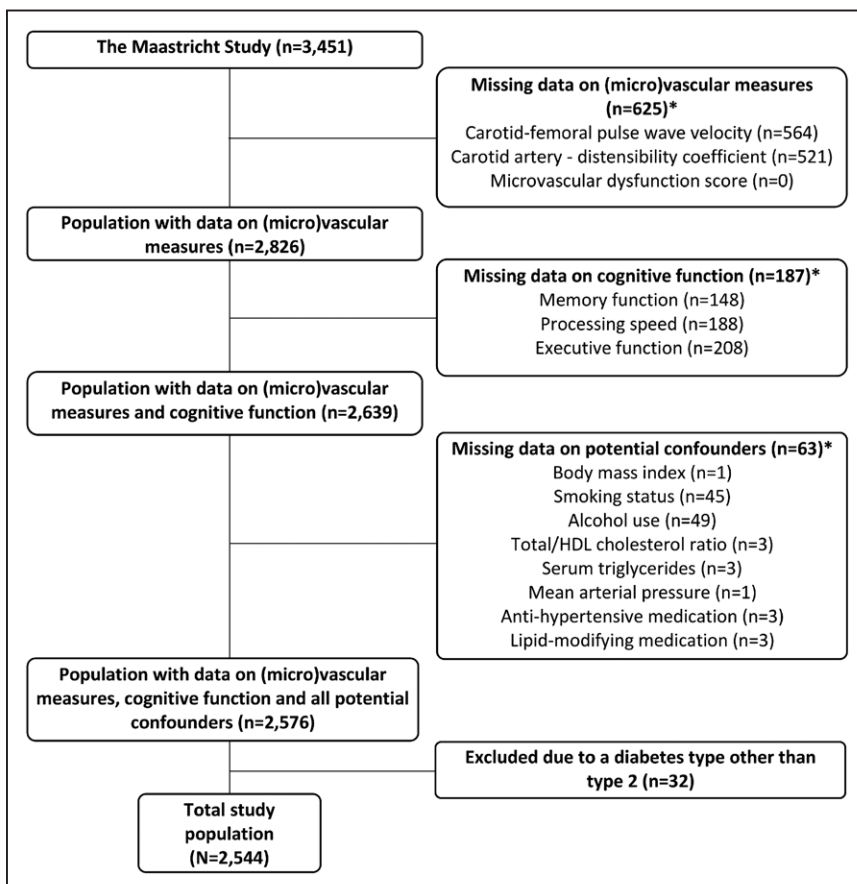
All analyses were performed with PASW software (version 22.0). A *P* value of <0.05 was considered statistically significant.

### Results

Figure 1 shows the derivation of the study population. In total, 2544 participants had data available on arterial stiffness, at least one MVD measure, the cognitive function score, and all potential confounders. Table 1 shows the characteristics of the study population and according to tertiles of the cognitive function score. Characteristics of the individuals excluded from the analyses due to missing values are provided in Table S1. On average, excluded individuals were older, more often male, had received lower education and had a worse cardiovascular risk profile. The study population for the present analyses had a mean age of 59.7 years, 51.0% were men, 26.0% had diabetes mellitus type 2 (oversampled by design) and 41.5% had received a high education.

Higher cfPWV (per m/s) was associated with a lower cognitive function score (per SD;  $\beta$ , -0.018 [95% CI, -0.036 to -0.000]) after adjustment for confounders but without adjustment for the MVD score (Table 2; Model 3). This effect of cfPWV on cognitive performance was equivalent to 0.35 years of aging for each m/s higher cfPWV. Results were similar after additional adjustments for prior cardiovascular disease, low-grade inflammation, and current depression (Table 2, Model 4). CarDC was not associated with the cognitive function score after full adjustment for confounders (Table 2).

Mediation analysis showed that higher cfPWV (per m/s) was associated with a higher MVD score (per SD;  $\beta$ , 0.034



**Figure 1.** Derivation of the study population. \*Missings not mutually exclusive.

Table 1. Study Characteristics

Study Characteristics	Total Population (n=2544)	Teriles of Cognitive Function Score		
		Lowest (n=848)	Middle (n=848)	Highest (n=848)
Age, y	59.7±8.1	64.1±6.7	60.2±7.1	54.9±7.7
Men	51.0 (1297)	63.7 (540)	53.2 (451)	36.1 (306)
Education				
Low	15.4 (393)	29.7 (252)	12.4 (105)	4.2 (36)
Intermediate	43.1 (1096)	45.3 (384)	45.5 (386)	38.4 (326)
High	41.5 (1055)	25.0 (212)	42.1 (357)	57.3 (486)
Glucose metabolism status				
Normal glucose metabolism	58.8 (1496)	42.6 (361)	59.9 (508)	73.9 (627)
Prediabetes	15.2 (387)	16.7 (142)	15.7 (133)	13.2 (112)
Type 2 diabetes mellitus	26.0 (661)	40.7 (345)	24.4 (207)	12.9 (109)
Body mass index, kg/m <sup>2</sup>	26.9±4.4	27.8±4.3	26.9±4.5	26.1±4.1
Current smokers	13.4 (342)	15.9 (135)	12.5 (106)	11.9 (101)
High alcohol consumption (women >7; men >14 U/wk)	26.9 (684)	23.6 (200)	27.0 (229)	30.1 (255)
Total cholesterol/high-density lipoprotein ratio	3.7±1.2	3.8±1.2	3.8±1.2	3.6±1.2
Office mean arterial pressure, mm Hg	96.6±10.2	98.2±10.6	97.1±9.7	94.7±10.1
Heart rate, bpm	62.5±9.3	63.0±9.8	62.0±9.0	62.6±9.0
Antihypertensive medication use	37.7 (959)	53.7 (455)	35.7 (303)	23.7 (201)
Lipid-modifying medication use	35.1 (893)	49.5 (420)	35.1 (298)	20.6 (175)
Prior cardiovascular disease	16.2 (405)	24.5 (204)	14.7 (123)	9.3 (78)
Current depression	3.5 (88)	4.8 (40)	3.6 (30)	2.1 (18)
Plasma biomarkers of low-grade inflammation composite score, SD	0.0±1.0	0.2±0.7	0.0±0.6	-0.2±0.6
Measures of arterial stiffness				
Carotid-femoral pulse wave velocity, m/s	9.0±2.1	9.7±2.4	8.9±2.0	8.3±1.7
Carotid distensibility coefficient, 10 <sup>-3</sup> /kPa	14.3±5.1	12.9±4.7	14.2±4.8	15.9±5.3
Measures of microvascular dysfunction*				
Microvascular dysfunction score, SD	0.0±1.0	0.4±1.2	-0.1±0.8	-0.3±0.7
Total brain parenchyma volume, mL	1136±111	1123±113	1146±117	1137±103
White matter hyperintensity volume, mL	0.2 (0.1–0.8)	0.4 (0.2–1.4)	0.3 (0.1–0.9)	0.1 (0.0–0.4)
Cerebral microbleeds	12.0 (203)	15.8 (79)	10.9 (64)	9.8 (60)
Lacunar infarcts	5.3 (91)	6.3 (32)	6.6 (39)	3.2 (20)
Flicker light-induced arteriolar dilation, %	3.1±2.8	2.7±2.9	3.1±2.8	3.3±2.8
Flicker light-induced venular dilation, %	3.9±2.2	3.7±2.1	3.9±2.2	4.0±2.3
Urinary albumin excretion ≥30 mg/24 h	7.5 (190)	12.4 (104)	6.1 (51)	4.1 (35)
Soluble intracellular adhesion molecule-1, ng/mL	352.6±96.8	372.4±116.3	349.2±85.9	336.4±81.1
Soluble vascular adhesion molecule-1, ng/mL	425.4±98.1	447.1±111.3	423.1±94.4	406.2±82.1
Soluble E-selectin, ng/mL	117.1±64.8	130.2±79.1	116.9±55.2	104.1±54.4
Von Willebrand Factor, %	131.8±47.2	141.4±50.1	131.0±45.7	123.2±43.9

Data presented as mean±SD, median (interquartile range), or n (%).

\*The microvascular dysfunction score was calculated when data were available on at least one individual microvascular dysfunction measure. For an explanation of the calculation of this score, see text. Data available for total brain parenchyma volume, n=1726; white matter hyperintensity volume, n=1726; cerebral microbleeds, n=1697; lacunar infarcts, n=1724; flicker light-induced arteriolar dilation, n=1649; flicker light-induced venular dilation, n=1679; urinary albumin excretion, n=2522; soluble intercellular adhesion molecule-1, n=2520; soluble vascular adhesion molecule-1, n=2520; soluble E-selectin, n=2520; von Willebrand factor, n=2517.

[95% CI, 0.014 to 0.053]), and that a higher MVD score (per SD) was associated with a lower cognitive function score (per SD;  $\beta$ , -0.089 [95% CI, -0.124 to -0.053]; Figure 2). When

we additionally adjusted the association between cfPWV and the cognitive function score for the MVD score, the direct association was attenuated and no longer statistically significant.

**Table 2. Associations Between Arterial Stiffness and Cognitive Function**

Arterial Stiffness Measure	Model	Cognitive Function Score, Per SD	
		$\beta$ (95% CI)	P Value
Carotid-femoral pulse wave velocity, m/s	1	-0.032 (-0.048 to -0.016)	<0.001
	2	-0.019 (-0.035 to -0.003)	0.02
	3	-0.018 (-0.036 to -0.000)	0.04
	4*	-0.019 (-0.037 to -0.001)	0.04
Carotid distensibility coefficient, 10 <sup>-3</sup> /kPa	1	-0.007 (-0.014 to -0.000)	0.04
	2	-0.005 (-0.012 to 0.002)	0.15
	3	-0.004 (-0.012 to 0.003)	0.28
	4*	-0.004 (-0.012 to 0.003)	0.32

Model 1: adjusted for age, sex, education, Model 2: Model 1+ glucose metabolism status, body mass index, smoking, alcohol use, total/high-density lipoprotein cholesterol ratio and triglycerides, and Model 3: Model 2+ mean arterial pressure, heart rate and use of anti-hypertensive and/or lipid-modifying medication. Model 4: Model 3+ prior cardiovascular disease, low-grade inflammation, and current depression. \*Data on prior cardiovascular disease, low-grade inflammation, and current depression available in n=2482. The standardized regression coefficients in model 3 were for carotid-femoral pulse wave velocity -0.039 (95% CI, -0.078 to -0.001) and for carotid distensibility coefficient -0.021 (95% CI, -0.060 to 0.017).

The indirect effect explained by the MVD score was statistically significant ( $\beta$ , -0.0030 [95% CI, -0.0057 to -0.009]) and was 16.2% of the total effect of cfPWV on the cognitive function score (Figure 2). CarDC was not associated with a higher MVD score, and the MVD score did not statistically significantly mediate the association between CarDC and the cognitive function score (Figure S2).

We found no interactions with age, sex, education, and glucose metabolism status (*P* values for interaction >0.05).

The results of the additional analyses are given in the Item S5 and Tables S2 to S8.

### Discussion

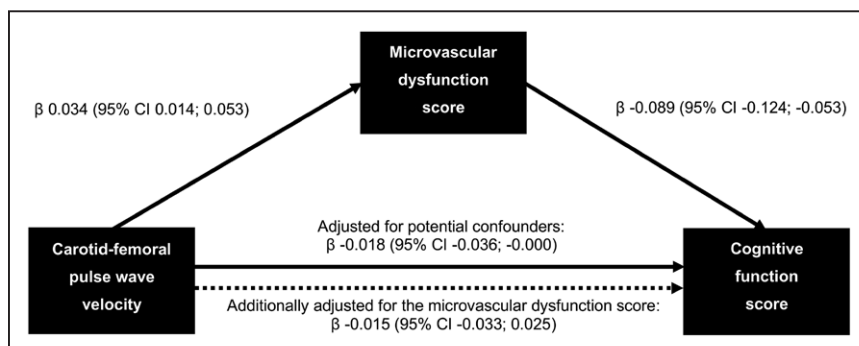
In this cross-sectional study, higher aortic stiffness, but not carotid stiffness, was associated with worse cognitive performance. In addition, the association between aortic stiffness and cognitive performance was in part (16.2%) explained or mediated by a composite score of various MVD measures, including CSVD features, flicker light-induced retinal arteriolar and venular dilation response, UAE, and plasma biomarkers of MVD.

The study findings are in accordance with the hypothesis that higher aortic stiffness increases the risk of worse cognitive performance in part via MVD.<sup>3</sup> Higher aortic stiffness may lead to cerebral MVD via an increased pulsatile load on the microcirculation. This increased load may cause direct microvascular damage and may induce a microvascular

remodeling response. This response initially serves to limit the penetration of the pulsatile load into the microvasculature by raising vascular resistance.<sup>3</sup> However, this protective response may ultimately become unfavorable, leading to cerebral hypoperfusion, impaired neurogenesis and vasoreactivity, and blood-brain barrier hyperpermeability.

Previous studies have shown associations between higher cfPWV with various MVD measures, including MRI features of CSVD<sup>18</sup> and albuminuria.<sup>33,34</sup> In addition, previous studies have shown an association between various MVD measures (ie, CSVD features, albuminuria, and plasma biomarkers of MVD) and worse cognitive performance,<sup>22,35-39</sup> and between higher cfPWV and worse cognitive performance.<sup>4-18,21</sup> However, only one previous study<sup>21</sup> evaluated arterial stiffness, cognitive performance, and MVD at the same time. This study found an association between higher cfPWV and worse memory and showed that this association was attenuated after adjustments for higher white matter hyperintensity volume.<sup>21</sup> The present study extends previous research by showing, with use of a formal mediation analysis, that the association between higher cfPWV and worse cognitive performance is in part mediated, or explained, by a composite score of various direct and indirect measures of MVD. It thereby provides additional evidence consistent with the role of arterial stiffness as a contributor to MVD and cognitive decline.

Surprisingly, carotid stiffness was not associated with worse cognitive performance in our study, although the 95%



**Figure 2.** Association between carotid-femoral pulse wave velocity (per m/s) and cognitive function (per SD), and the mediating effect by microvascular dysfunction. The mediating effect by the microvascular dysfunction score (per SD) was -0.0030 (95% CI, -0.0057 to -0.009), corresponding to 16.2% of the total effect of carotid-femoral pulse wave velocity on cognitive performance. Solid lines indicate statistically significant associations; dashed lines nonstatistically significant associations. Adjustments as in Table 2, model 3.

CIs of the effect estimates do not exclude the possibility of such an association. In contrast, we previously found, in a smaller dataset of The Maastricht Study of the first 866 individuals included in the study, that is, from November 2010 to March 2012, that greater carotid stiffness was weakly associated with worse cognitive performance.<sup>17</sup> We cannot fully explain this difference, although it may be related to the slightly different characteristics of the 2 data samples. Although individuals included in the first study period were of the same age (60 years), they were more often men (54.6% versus 51.0%) and had a slightly worse cardiovascular risk profile, that is, had more often type 2 diabetes mellitus (27.2% versus 26.0%), were more often current smokers (15.9% versus 13.4%), and more often had high alcohol consumption (30.9% versus 26.9%) and prior cardiovascular disease (17.2% versus 16.2%). Although both analyses adjusted for these potential confounders, we cannot exclude the possibility of residual confounding. In addition, we cannot exclude that the difference in results are due to the play of chance. Seven other studies<sup>12–16,19,20</sup> evaluated the association between carotid stiffness and cognitive performance or dementia and also had inconsistent results. Some,<sup>12–14,16</sup> but not all,<sup>15,19,20</sup> found an association between higher carotid stiffness and worse cognitive performance or dementia. These conflicting results may be due to the differences in cognitive tests used and inconsistent adjustments for potential confounders (eg, only one study<sup>15</sup> adjusted for heart rate and 2 studies<sup>15,19</sup> for [mean] arterial blood pressure, whereas other studies<sup>12–14,16,19,20</sup> did not). The association between carotid stiffness and cognitive performance, therefore, remains unclear. It is possible that only disproportionate stiffening of the (proximal) aorta contributes to subsequent transmission of increased pulsatile energy to the brain but not stiffening of the carotid arteries,<sup>20</sup> and this issue requires further study.

Only a relatively small part of the association between cFPWV and cognitive performance was explained by MVD, and the clinical significance of this mediating effect is unclear. This relatively small effect may be explained by various reasons. First, this remaining association may be due to MVD that is not directly captured in our MVD score (eg, blood-brain barrier leakage and altered cerebrovascular reactivity). Second, it is possible that only part of cognitive impairment in aortic stiffness is due to MVD. Third, although we adjusted for a large set of potential confounders, we cannot exclude the possibility of residual confounding. Fourth, some individuals had missing data on individual components of the MVD score, which may have led to an underestimation of the mediating effect by MVD.

The present study gives insight in the pathophysiological mechanisms between arterial stiffness, MVD, and cognitive performance, which might help to design prevention strategies of cognitive impairment. Evidence suggests that lifestyle modifications, such as weight loss and exercise, may favorably influence arterial stiffness and MVD.<sup>1,40</sup> In addition, drugs, such as renin-angiotensin-aldosterone system inhibitors, antihyperglycemic agents (ie, metformin and glucagon-like peptide 1 receptor agonists), and statins, may improve arterial elasticity and microvascular function, possibly beyond their blood pressure-, glucose-, or lipid-lowering effects.<sup>1,40</sup>

Strengths of the present study are the large population-based sample, the comprehensive assessment of various measures of MVD, and the extensive characterization of participants, which enabled us to adjust for a series of potential confounders.

Our study has limitations. First, the cross-sectional observational design precludes reaching strong causal conclusions about the study findings. For instance, it is also possible that MVD contributes to large artery stiffness, for example, via increasing peripheral resistance and mean blood pressure, and via damage to the microvasculature of large arteries (vasa vasorum) themselves.<sup>1</sup> Second, the construction of the composite scores assumes that all its components either directly or indirectly reflect cerebral MVD, which is not necessarily true. The mechanisms underlying some markers may be heterogeneous and not necessarily indicative of MVD. However, results did not materially change after exclusion of individual MVD measures from the MVD score. Third, a relatively large number of statistical tests were done. The aim of the present study was to investigate the pathways by which various factors (arterial stiffness and MVD) may contribute to worse cognitive performance, which, as a consequence, involves carrying out multiple tests. Fourth, the study population consisted mostly of middle-aged participants without dementia who were relatively well educated and whose cardiovascular risk factors were relatively well controlled. This may have led to an underestimation of the reported findings due to lower variation in cognitive performance and relatively high cognitive reserve.

In conclusion, the present study found that aortic stiffness, but not carotid stiffness, is independently associated with worse cognitive performance, and that this association is in part explained by MVD.

## Perspectives

This study supports the hypothesis that MVD explains, in part, the association between aortic stiffness and worse cognitive performance. Future longitudinal studies are needed to evaluate the association of arterial stiffness, MVD, and cognitive decline and dementia.

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## Disclosures

None.

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## Novelty and Significance

### What Is New?

- We tested, with use of a formal mediation analysis, whether the association between higher arterial stiffness and worse cognitive performance is mediated, or explained, by microvascular dysfunction, in a large population-based study.
- Microvascular dysfunction was measured by MRI features of cerebral small vessel disease, flicker light-induced retinal arteriolar and venular dilation, albuminuria and plasma biomarkers of microvascular dysfunction.

### What Is Relevant?

- We found an association between higher aortic stiffness and worse cognitive performance.

- A composite score of microvascular dysfunction statistically significantly explained part of this association.

### Summary

- Our findings are consistent with the hypothesis that arterial stiffness is a contributor to microvascular dysfunction and worse cognitive performance.
- Future longitudinal studies are needed to further evaluate the association of microvascular dysfunction and cognitive decline and dementia.