Arterial stiffness and progression of structural brain changes

The SMART-MR study

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ABSTRACT

Objective: To examine the cross-sectional and prospective associations between arterial stiffness and structural brain changes within the Second Manifestations of Arterial Disease–Magnetic Resonance (SMART-MR) study, a prospective cohort study among patients with manifest arterial disease.

Methods: Distension measurements of the common carotid arteries and a brain MRI were performed in 526 patients (mean age 59 ± 10 years). After a mean follow-up of 4.1 years (range 3.6–5.8), brain MRI was repeated in 308 patients. Brain segmentation was used to quantify total brain volume, cortical gray matter volume, ventricular volume, and white matter lesion (WML) volume (relative to intracranial volume). Infarcts were rated visually.

Results: Cross-sectional multivariable regression analyses showed that 1 SD decrease in carotid distension, indicating increased arterial stiffness, was associated with smaller relative total brain and cortical gray matter volumes (B = −0.24%, 95% confidence interval [CI] −0.44 to −0.04%, and B = −0.47%, 95% CI −0.75 to −0.19%), with larger WML volume (B = 0.09%, 95% CI −0.01 to 0.19%), and with higher risk of having nonlacunar (cortical or large subcortical) brain infarcts (relative risk = 1.44, 95% CI 1.14 to 1.81). However, our prospective findings showed that carotid distension was not significantly associated with progression of brain atrophy, WML volume, or brain infarcts.

Conclusion: In this population of patients with manifest arterial disease, stiffening of the carotid arteries was cross-sectionally associated with more brain atrophy, WML volume, and nonlacunar infarcts, but did not lead to changes in brain volumes or infarcts after 4 years. ***Neurology*®** **2015;84:448–455**

GLOSSARY

ACE = angiotensin-converting enzyme; **ANCOVA** = analysis of covariance; **BA** = basilar artery; **BMI** = body mass index; **BP** = blood pressure; **CC** = compliance coefficient; **CI** = confidence interval; **CIMT** = carotid intima media thickness; **DC** = distensibility coefficient; **FLAIR** = fluid-attenuated inversion recovery; **ICA** = internal carotid artery; **ICV** = intracranial volume; **IR** = inversion recovery; **OR** = odds ratio; **pCBF** = parenchymal cerebral blood flow; **RR** = relative risk; **SMART-MR** = Second Manifestations of Arterial Disease–Magnetic Resonance; **TE** = echo time; **TI** = inversion time; **TR** = repetition time; **WML** = white matter lesion; **YEM** = Young's elastic modulus.

One of the hallmarks of the aging cardiovascular system is stiffening of the arterial wall. Arterial stiffness is related to age and cardiovascular risk factors, especially elevated blood pressure, smoking, obesity, and diabetes mellitus.[1] It can therefore be seen as a summary measure of vascular risk. Yet it also is an independent risk factor for myocardial infarction, cardiovascular death, and clinical stroke.[2–5]

It has been well established that cardiovascular risk factors play an important role in the development of cognitive decline and dementia.[6] Arterial stiffness may be among these factors.[7–10]

It has been suggested that particularly the small arteries of the brain are vulnerable to high pulsatile pressure and flow, caused by increased arterial stiffness.[11] This may contribute to cerebral small vessel disease and brain atrophy.[12] Also, stiffness of the large arteries may impair

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cerebral autoregulation, predisposing to hypoperfusion during hypotension, subsequently leading to ischemia.[13]

Several cross-sectional studies relating arterial stiffness to the subclinical markers of dementia showed a relation between increased arterial stiffness and larger white matter lesion (WML) volumes,[14–20] more lacunar infarcts,[14,20,21] more brain atrophy,[12,20] and lower cerebral perfusion.[22] However, it is unknown whether arterial stiffness contributes to an increased development of ischemic and degenerative brain changes over time. Also, no studies were performed in patients with manifest arterial disease, although they may be subject to early vascular aging.

We examined the cross-sectional and prospective relations of common carotid artery stiffness with presence and progression of brain atrophy, WML volume, and brain infarcts in patients with manifest arterial disease.

METHODS

SMART-MR study. The Second Manifestations of Arterial Disease–Magnetic Resonance (SMART-MR) study is a prospective cohort study in patients with manifest arterial disease with the aim to determine risk factors and consequences of brain aging. The design has been described elsewhere.[23–25] In brief, patients who came to the University Medical Center Utrecht with coronary artery disease, cerebrovascular disease, peripheral artery disease, or abdominal aortic aneurysm were invited to participate in the study between 2001 and 2005. All patients without contraindications underwent a 1.5T MRI of the brain; they also had a physical examination, ultrasonography of the carotid arteries, and blood sampling. Using questionnaires, risk factors, medical history, and functioning were assessed.

Carotid distension was measured from 2001 until 2003, when 554 patients were included. Of these, brain MRI data were available in 526 patients. After on average 4.1 years (range 3.6–5.8), 325 (59%) patients had follow-up measures, and a brain MRI was repeated in 308 patients.

Standard protocol approvals, registration, and patient consents. The ethics committee of our institution approved the SMART-MR study and written informed consent was obtained from all participants.

Arterial stiffness. Stiffness was measured by distension of both common carotid arteries. The distension of an artery is the change in diameter in systole relative to the diastolic diameter during the cardiac cycle. The displacement of the walls of the left and right common carotid artery was measured with a Wall Track System (Scanner 200, Pie Medical, Maastricht, the Netherlands) equipped with a 7.5-MHz linear array transducer and vessel wall moving detector system. Coefficients of variation for intraobserver and interobserver variability study of distension and end-diastolic lumen diameter measurements were all $<10\%$.[26] Adjusted carotid distension was the primary stiffness measure,[27] using blood pressure (BP) simultaneously measured at the brachial artery at 4-minute intervals. In addition, traditional indices of arterial stiffness were used for comparison. β stiffness index, compliance coefficient (CC), distensibility coefficient (DC), Peterson's modulus, and Young's elastic modulus (YEM) were calculated as described previously.[27] Increasing distension, CC, and DC indicate decreasing stiffness. Distensibility is the relative change in diameter and compliance is the absolute change in diameter with pressure. Peterson's (elastic) modulus is the pressure change required for (theoretical) 100% increase in diameter, and YEM is the pressure per square millimeter required for (theoretical) 100% extension.[28]

MRI protocol. This protocol has been described elsewhere.[29] At baseline and follow-up, the MRI was performed on a 1.5T whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, the Netherlands). The protocol consisted of transversal T1-weighted (repetition time [TR]/echo time [TE] 235/2 msec), T2-weighted (TR/TE = 2,200/11 msec and 2,200/100 msec), fluid-attenuated inversion recovery (FLAIR) (TR/TE/inversion time [TI] = 6,000/100/2,000 msec), and inversion recovery (IR) (TR/TE/TI = 2,900/22/410 msec) sequences. Field of view was 230 × 230 mm, matrix size 180 × 256, slice thickness 4.0 mm, no gap, 38 slices. On the basis of a localizer magnetic resonance angiographic slab in the sagittal plane, a 2D phase-contrast section was positioned at the level of the skull base to measure the volume flow in the internal carotid arteries (ICAs) and the basilar artery (BA). The 2D phase-contrast section was positioned through the ICAs and the BA (TR/TE = 16/9 msec; flip angle, 7.5°; field of view, 250 × 250 mm; matrix size, 256 × 256; slice thickness, 5.0 mm; 8 acquired signals; velocity sensitivity, 100 cm/s).[29]

Brain segmentation. The brain segmentation has been described elsewhere.[29] We used the T1-weighted gradient-echo, IR sequence, and FLAIR sequence for the probabilistic segmentation technique.[30,31] We also visually checked the results of the segmentation analysis for the presence of infarcts and infarct volumes were manually segmented to distinguish them from WML. Volumes of gray matter, white matter, WML, and infarct volumes were summed to obtain total brain volume, which then was summed with sulcal and ventricular CSF to obtain intracranial volume (ICV). Total brain, cortical gray matter, and ventricular volume were normalized for ICV (%).

At baseline and follow-up, infarcts were rated visually by an investigator and a neuroradiologist blind to clinical characteristics, and were defined as focal hyperintensities on T2-weighted images of >3 mm in diameter. If hyperintensities appeared in the white matter, they also had to be hypointense on T1-weighted and FLAIR images to differentiate them from WML. We differentiated infarcts from dilated perivascular spaces based on location, form, and absence of gliosis. We categorized infarcts as lacunar (3–15 mm) and nonlacunar (cortical infarcts, large subcortical infarcts). Volumes of WML were normalized for ICV (%).

Cardiovascular risk factors. We measured BP twice in a sitting position with a sphygmomanometer and the average of the 2 measurements was calculated. Mean arterial pressure and pulse pressure were calculated. Hypertension was defined as BP >140/90 mm Hg or use of antihypertensive drugs. Body mass index (BMI) was calculated (kg/m^2). Diabetes mellitus was defined as a history of diabetes, a fasting glucose level of ≥7.0 mmol/L, or use of glucose-lowering agents. Hyperlipidemia was defined as fasting total cholesterol >5.0 mmol/L, fasting low-density lipoprotein cholesterol >3.2 mmol/L, or use of lipid-lowering drugs. Smoking habits and alcohol intake were categorized as never, former, or current. Carotid intima media thickness (CIMT) of the common carotid arteries was measured using ultrasonography and the degree of carotid artery stenosis in the ICAs using color Doppler-assisted duplex scanning. Carotid artery stenosis ≥70%

was defined as peak systolic velocity >210 cm/s, since this was found before to be the best parameter.[32] Total parenchymal cerebral blood flow (pCBF) was calculated by summing the flow through the left and right ICAs and BA (mL/min) per 100 mL brain parenchymal volume.[29]

Data analyses. We used multiple imputation (10 datasets) to address missing values (table 1) using the statistical program R (aregImpute) (version 2.10.0).[33] Data were analyzed using SPSS version 20.0 (Chicago, IL), by pooling the 10 imputed datasets.

First, linear regression analyses and analysis of covariance (ANCOVA) were used to investigate the cross-sectional associations of measures of carotid stiffness (continuous and tertiles) with baseline relative total brain, cortical gray matter, ventricular, and total WML volume. We estimated relative risks (RR) rather than odds ratios (OR), which are likely to overestimate the RR in cohort studies, particularly for outcomes that are common.[34] Using Poisson regression with robust standard errors, we estimated cross-sectional associations of carotid stiffness with presence of lacunar and nonlacunar brain infarcts. The primary measure of carotid stiffness was distension, divided by the SD of the mean population. Additionally, analyses were performed for the other indexes of arterial stiffness (DC, β-index, CC, Peterson's modulus, YEM). All analyses were adjusted for age and sex, and, if not yet included in the calculation of the arterial stiffness measure, for carotid end-diastolic diameter and mean arterial pressure (model 1). In model 2, we additionally adjusted for smoking, alcohol, BMI, antihypertensive treatment, hyperlipidemia, diabetes, and CIMT. In model 3, we also adjusted for concomitant vascular brain lesions (for analyses with brain volumes) or brain volume (for analyses with WML volume and brain infarcts).

Second, regression analyses and ANCOVA were used to investigate the prospective associations of carotid stiffness (continuous and tertiles) with change in brain MRI measures, by using the brain volume and WML volume measures and progression of lacunar and nonlacunar brain infarcts at follow-up as dependent variable, and stiffness parameters and the respective volumes or infarcts at baseline as independent variable. Progression of infarcts was defined as patients with ≥1 new infarct vs no new infarct during follow-up. Analyses were adjusted using the same models as described above, with inclusion of follow-up time.

Third, to evaluate whether age, hypertension, antihypertensive treatment, CIMT, or pCBF were effect modifiers, interaction terms were entered and, if considered significant ($p < 0.10$), stratified analyses were performed (categories or median split), except for infarcts, due to limited power.

Finally, to further explore the role of antihypertensive treatment on the prospective associations, we additionally adjusted for increase in number of antihypertensive drugs during follow-up.

RESULTS Mean (SD; range) age of the total study population at baseline (n = 526) was 59 (10; 29–82) years and 83% were men. Patients with follow-up measurements (n = 308) were somewhat younger, had less stiff arteries, and had slightly smaller CIMT as indicated from the descriptives in table 1. BP measures were similar for both groups (table 1).

Cross-sectional analyses. Lower carotid distension (indicating increased carotid stiffness) was related to smaller relative total brain and cortical gray matter volume, with larger relative WML volume, and with more nonlacunar brain infarcts, but not with relative ventricular volume or lacunar infarcts (table 2). Further adjustments for cardiovascular risk factors and carotid atherosclerosis (model 2) or concurrent vascular brain lesions or brain volume at baseline slightly attenuated the observed associations: B (95% confidence interval [CI]) became −0.20% (−0.40; −0.01%) for total brain volume, −0.34% (−0.61; −0.07%) for cortical gray matter volume, and 0.08% (−0.02; 0.17) for WML volume (model 3). The RR for nonlacunar infarcts became 1.37 (95% CI 1.10–1.72). The adjusted R^2 of model 2 including distension ranged from 0.29 for total WML volume to 0.48 for total brain volume; however, only a small part of the total R^2 was explained by distension (between 0.003 and 0.017). Comparable associations were found for the other indices of arterial stiffness (table 2).

Age, hypertension, and CIMT significantly modified the association between carotid distension and relative total brain volume (p values were 0.059, 0.071, and 0.009, respectively), with stronger associations in older patients, patients with uncontrolled hypertension, and patients with larger CIMT (table e-1 on the *Neurology*® Web site at Neurology.org). Also, age significantly modified the association between carotid distension and relative WML volume (p value was 0.006), with a stronger association in older patients (table e-1).

When repeating the cross-sectional analyses in the 308 patients with follow-up data, the effect estimates were similar for brain volumes and nonlacunar infarcts, but disappeared for total WML volume: B (95% CI) for total brain, cortical gray matter, and total WML volume were −0.28% (−0.54; −0.03%), −0.56% (−0.92; −0.19%), and 0.06% (−0.08; 0.20%). The RR (95% CI) for nonlacunar infarcts became 1.48 (1.05; 2.09) (model 1).

Prospective analyses. After a mean (SD; range) follow-up of 4.1 (0.3; 3.6–5.8) years, mean (SD) relative total brain volume and cortical gray matter volume decreased with 1.1% (1.2%) and 2.0% (2.2%), and mean (SD) ventricular and WML volume increased with 0.2% (0.3%) and 0.1% (0.3%). At follow-up, there were 51 new lacunar infarcts in 26 patients, and 23 new nonlacunar infarcts in 14 patients. All secondary preventive treatment increased during follow-up; particularly angiotensin-converting enzyme (ACE) inhibitors and β-blockers increased in the lowest distension tertile (table e-2).

Carotid distension (continuous or tertiles) was not significantly related to changes in total brain, cortical gray matter, or ventricular volume, nor with changes in WML volume. An association was found with lower carotid distension and less progression of nonlacunar brain infarcts, and increasing YEM was associated with more progression of lacunar infarcts, but these relations were not found for the other stiffness measures (table 3).

Table 1 Baseline characteristics of the total study sample after imputation (n = 526) and the study sample with follow-up measurements (n = 308)

	Total study sample (n = 526)	Study sample with follow-up (n = 308)
Demographics		
Male sex	83	83
Age, y	59 ± 10	57 ± 9
Carotid stiffness		
Distension, mm	0.44 ± 0.15	0.46 ± 0.14
End-diastolic diameter carotid artery, mm	7.92 ± 1.04	7.84 ± 0.95
Distensibility coefficient, $kPa^{-1} \times 10^{-3}$	15.3 ± 6.4	15.9 ± 6.2
β stiffness index	11.0 ± 5.5	10.3 ± 4.2
Compliance coefficient, mm^2/kPa	0.74 ± 0.33	0.76 ± 0.32
Peterson's modulus, $kP \times 10^2$	1.60 ± 0.86	1.49 ± 0.68
Young's modulus, $kPa \times 10^3$	0.68 ± 0.38	0.65 ± 0.29
Arterial disease categories		
Coronary artery disease	62	65
Cerebrovascular disease	25	24
Peripheral artery disease	20	17
Abdominal aortic aneurysm	8	6
Vascular risk factors		
Body mass index, kg/m^2	27 ± 4	27 ± 4
Smoking, current	27	23
Alcohol, current	74	79
Diabetes mellitus	21	19
Hyperlipidemia	77	77
Blood pressure measures		
Systolic blood pressure, mm Hg	140 ± 22	140 ± 21
Diastolic blood pressure, mm Hg	81 ± 11	81 ± 11
Pulse pressure, mm Hg	59 ± 15	59 ± 15
Mean arterial pressure, mm Hg	101 ± 14	101 ± 13
Antihypertensive medication	62	64
Carotid atherosclerosis		
Intima media thickness, mm	0.96 ± 0.34	0.93 ± 0.28
Carotid stenosis >50	19	19
Carotid stenosis >70	14	14
Cerebral blood flow		
Total, mL/min	602 (131)	605 (25)
Parenchymal, mL/min/100 mL	52 (11)	52 (10)
Vascular brain lesions		
White matter lesion volume, mL	1.6 (0.4–9.2)	1.4 (0.4–5.9)
Presence of lacunar infarcts	21	20
Presence of nonlacunar infarcts	16	15

Continued

Interaction terms and stratified analyses did not suggest any effect modification. Stratifying for hypertension status (no/controlled/uncontrolled) and additional adjustment for increase in number of antihypertensive drugs did not change the results (data not shown).

DISCUSSION In a population with manifest arterial disease, increased arterial stiffness was cross-sectionally associated with more brain atrophy and more vascular brain lesions, independent of vascular risk factors, and only partly explained by (other) cerebrovascular lesions. However, prospective analyses showed that increased arterial stiffness was not associated with progression of brain atrophy, WML volume, or brain infarcts after 4 years of follow-up.

The cross-sectional findings are largely in agreement with previous studies in the general population, which reported that higher aortic or carotid stiffness was associated with larger WML volume,[12,16,19,20] and that increased carotid stiffness was associated with smaller total and gray and white matter volume.[12] However, in previous studies the association between aortic stiffness and lacunar or silent subcortical brain infarcts was inconsistent, and no association was found with cortical infarcts.[12,16,19,20]

In our study, the associations were stronger in older patients, in patients with uncontrolled hypertension, and in patients with larger CIMT. Since these are factors related to endothelial dysfunction and atherosclerosis,[35] it suggests that, together with arterial stiffness, these are among the conditions that may aggravate brain damage. The associations between arterial stiffness and more brain atrophy or WML volume could partly be explained by damage to the small cerebral arteries, caused by the high pulsatile pressure and flow as a consequence of increased arterial stiffness.[11] This is indeed suggested by our finding that adjustments for vascular brain lesions slightly attenuated the associations. Also, impaired cerebral autoregulation, predisposing to hypoperfusion during hypotension, subsequently leading to ischemia, could play a role.[13] However, we did not find that pCBF modified the association. Finally, arterial stiffness has been associated with increased amyloid-β plaque depositions, which could induce brain atrophy.[36]

To our knowledge, this is the first study that examined the prospective relations of arterial stiffness with progression of brain atrophy, WML volume, and brain infarcts. One previous study in a community-dwelling older population found that increased aortic stiffness was associated with larger WML volume 10 years later, although the authors did not report on change in WML volume over time.[18] Although we do not have a sound explanation for the disparity between the cross-sectional and prospective findings, there are some suggestions. First, it is

Table 1 Continued

	Total study sample (n = 526)	Study sample with follow-up (n = 308)
Brain volumes		
Total brain volume (ICV)	78.8 ± 2.9	79.1 ± 2.6
Cortical gray matter volume (ICV)	36.1 ± 3.4	36.3 ± 3.0
Ventricular volume (ICV)	2.2 ± 1.0	2.1 ± 0.09

Abbreviation: ICV = intracranial volume.
Values are %, mean ± SD, or median (10th–90th percentile). Percentage of missing values before imputation: diabetes mellitus and hyperlipidemia, 2.9%; smoking and alcohol use, 1.6%; antihypertensive treatment, 1.0%; carotid intima media thickness, 1.3%; carotid stenosis, 3.2%; cortical gray matter volume, 21.3%; all other variables, 0.0%.

possible that only severe arterial stiffness contributes to brain changes. Compared to a population-based older population, arterial stiffness was mild in our population,[16] and possibly not severe enough to lead to brain pathology. Second, we examined carotid stiffness, which may reflect an earlier stage than aortic stiffness.[37] Although carotid stiffness is preferred as an early marker for vascular disease,[37] the predictive value may be delayed and a longer follow-up period between the 2 brain MRIs may be needed to find an association between carotid stiffness and progression of brain damage. Third, all preventive treatment intensified during follow-up, especially ACE inhibitors and β-blockers in the patients with stiffest arteries (table e-2). This might have decreased arterial stiffness and thereby prevented further progression of brain damage.[38] Data on change in stiffness were not available, so we could not verify this. Yet stratifying by hypertension status and adjusting for increase in number of antihypertensive drugs as a measure of intensified treatment did not change the results. Also, antihypertensive treatment was not associated with brain changes, so this could not fully explain the lack of prospective associations. Fifth, it could be that arterial stiffening on the one hand, and brain lesions on the other hand, are independent processes with common elements in the causal pathway,[13] since many of the contributing factors in arterial stiffness are also potential contributors in brain aging and cognitive decline. Common pathophysiologic elements include hypertension, hyperlipidemia, impaired glucose metabolism, inflammation, and genetic factors.[1,6,39] Although adjustments for vascular risk factors did not materially change the cross-sectional associations, this explanation cannot be ruled out since residual confounding might be present.

This study is not without limitations. First, since a considerable proportion of the cohort did not participate at follow-up, it is possible that selective loss to follow-up of unhealthier persons explained the disparity between the cross-sectional and prospective analyses. However, since the cross-sectional results showed

Table 2 Cross-sectional relation between baseline carotid arterial stiffness and baseline brain volume or baseline vascular brain lesions

	Total brain volume (% ICV), B (95% CI)	Cortical gray matter volume (% ICV), B (95% CI)	Ventricular volume (% ICV), B (95% CI)
Decline in distension[a,b]	−0.24 (−0.44; −0.04)*	−0.47 (−0.75; −0.19)**	0.02 (−0.06; 0.10)
Distensibility coefficient[c]	−0.03 (−0.07; 0.00)	−0.08 (−0.13; −0.02)**	0.00 (−0.01; 0.02)
β stiffness index[c]	−0.05 (−0.09; −0.01)**	−0.07 (−0.13; −0.02)**	0.01 (−0.00; 0.03)
Compliance coefficient[c]	−0.36 (−0.94; 0.22)	−0.53 (−1.35; 0.30)	0.04 (−0.20; 0.27)
Peterson's modulus[c]	−0.30 (−0.55; −0.06)*	−0.44 (−0.80; −0.08)*	0.07 (−0.03; 0.17)
Young's modulus[c,d]	−0.38 (−0.86; 0.11)	−0.71 (−1.42; 0.00)	0.10 (−0.10; 0.30)
	ln total WML volume (% ICV), B (95%CI)	**Lacunar infarcts (n = 113),[e] RR (95%CI)**	**Nonlacunar infarcts (n = 82),[e] RR (95%CI)**
Decline in distension[a,b]	0.09 (−0.01; 0.19)	1.01 (0.83; 1.23)	1.44 (1.14; 1.81)**
Distensibility coefficient[c]	0.02 (0.00; 0.04)*	1.03 (0.99; 1.08)	1.08 (1.03; 1.14)**
β stiffness index[c]	0.02 (0.01; 0.04)*	1.02 (1.01; 1.04)**	1.03 (1.01; 1.05)**
Compliance coefficient[c]	0.11 (−0.18; 0.39)	1.43 (0.78; 2.63)	2.58 (1.11; 5.98)*
Peterson's modulus[c]	0.15 (0.03; 0.27)	1.24 (1.09; 1.40)**	1.30 (1.12; 1.51)**
Young's modulus[c,d]	0.27 (0.01; 0.52)*	1.38 (1.19; 1.60)**	1.43 (1.23; 1.67)**

Abbreviations: CI = confidence interval; ICV = intracranial volume; RR = relative risk; WML = white matter lesion.
Adjusted for age, sex, and cardiovascular risk factors.
[a] Per SD = 149 μm.
[b] In model 1, we additionally adjusted for diastolic diameter of the carotid artery and mean arterial pressure (these were already included in the calculation of the other indices of arterial stiffness).
[c] Distensibility coefficient and compliance coefficient are given per 1 unit decrease, and β stiffness index, Peterson's modulus, and Young's modulus are given per 1 unit increase so that all measures indicate more stiffness.
[d] In model 2, we did not adjust for intima media thickness since this was included in the calculation of Young's elastic modulus.
[e] The n means the number of patients with 1 or more lacunar or nonlacunar infarcts.
*$p < 0.05$; **$p < 0.01$.

Table 3 Prospective relation between baseline carotid arterial stiffness and change in brain volume or vascular brain lesions

	Progression of total brain volume (% ICV), B (95% CI)	Progression of cortical gray matter volume (% ICV), B (95% CI)	Progression of ventricular volume (% ICV), B (95% CI)
Decline in distension[a,b]	0.04 (−0.10; 0.18)	−0.05 (−0.34; 0.23)	−0.01 (−0.04; 0.03)
Distensibility coefficient[c]	0.01 (−0.02; 0.03)	0.01 (−0.04; 0.06)	−0.00 (−0.01; 0.00)
β stiffness index[c]	0.00 (−0.03; 0.03)	−0.02 (−0.09; 0.05)	0.00 (−0.01; 0.01)
Compliance coefficient[c]	0.16 (−0.23; 0.56)	−0.07 (−0.88; 0.74)	0.05 (−0.05; 0.15)
Peterson's modulus[c]	−0.01 (−0.22; 0.20)	−0.10 (−0.53; 0.34)	−0.01 (−0.06; 0.05)
Young's modulus[c,d]	−0.27 (−0.73; 0.19)	−0.64 (−1.61; 0.33)	0.05 (−0.08; 0.17)
	Progression of ln total WML volume (% ICV), B (95% CI)	**Progression of lacunar infarcts (n = 26),[e] RR (95% CI)**	**Progression of nonlacunar infarcts (n = 14),[e] RR (95% CI)**
Decline in distension[a,b]	−0.07 (−0.16; 0.01)	1.36 (0.83; 2.23)	0.63 (0.40; 0.99)*
Distensibility coefficient[c]	−0.01 (−0.03; 0.00)	1.11 (0.99; 1.25)	0.97 (0.88; 1.07)
β stiffness index[c]	−0.02 (−0.04; 0.00)	1.06 (0.98; 1.14)	0.97 (0.83; 1.32)
Compliance coefficient[c]	0.00 (−0.25; 0.26)	1.55 (0.36; 6.72)	2.71 (0.45; 16.52)
Peterson's modulus[c]	−0.06 (−0.19; 0.07)	1.43 (0.91; 2.23)	0.93 (0.32; 2.76)
Young's modulus[c,d]	−0.19 (−0.49; 0.11)	2.98 (1.03; 8.56)*	0.28 (0.05; 1.57)

Abbreviations: CI = confidence interval; ICV = intracranial volume; RR = relative risk; WML = white matter lesion.
Adjusted for age, sex, and cardiovascular risk factors.
[a] Per SD = 149 μm.
[b] We additionally adjusted for diastolic diameter of the carotid artery and mean arterial pressure (these were already included in the calculation of the other indices of arterial stiffness).
[c] Distensibility coefficient and compliance coefficient are given per 1 unit decrease, and β stiffness index, Peterson's modulus, and Young's modulus are given per 1 unit increase so that all measures indicate more stiffness.
[d] In model 2, we did not adjust for intima media thickness since this was included in the calculation of Young's elastic modulus.
[e] The n means the number of patients with ≥1 new infarct vs no new infarct during follow-up.
* $p < 0.05$.

similar effect estimates, except for WML, within the 308 patients with complete follow-up, this does not completely explain our findings. An alternative explanation could be that limited power for the prospective analyses partly explained this disparity. Second, we used carotid distension as a measure of arterial stiffness, whereas most studies used carotid-femoral pulse wave velocity measuring aortic stiffness. In healthy individuals the aorta and carotid artery stiffen in a similar rate with aging. Yet, with age and other cardiovascular risk factors, the carotid artery stiffens less than the aorta in patients with hypertension or diabetes.[40] Third, since our population consists of patients with manifest arterial disease, the results may not be applicable to the general population. Also, the extent of stiffness could be underestimated, causing an underestimation of the observed associations.

Strengths of our study include the prospective design and the volumetric assessment of brain segmentation of different brain tissue types, which made it possible to differentiate between cortical gray matter and ventricular and WML volume. Finally, the extensive information on cardiovascular risk factors and markers of vascular brain lesions allowed us to investigate whether the associations were independent of these factors.

In this population of patients with manifest arterial disease, stiffening of the carotid arteries was cross-sectionally associated with more brain atrophy, WML volume, and nonlacunar infarcts, but did not lead to changes in brain structure after 4 years.

AUTHOR CONTRIBUTIONS

Dr. H.M. Jochemsen: drafting/revising the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; statistical analysis. Dr. M. Muller: drafting/revising the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; statistical analysis; obtaining funding. M.L. Bots: drafting/revising the manuscript for content, including medical writing for content; analysis or interpretation of data. P. Scheltens: drafting/revising the manuscript for content, including medical writing for content. K.L. Vincken: drafting/revising the manuscript for content, including medical writing for content. W.P.T.M. Mali: drafting/revising the manuscript for content, including medical writing for content; study concept or design. Y. van der Graaf: study supervision or coordination; drafting/revising the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; acquisition of data; obtaining funding. M.I. Geerlings: study supervision or coordination; drafting/revising the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; acquisition of data.

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DISCLOSURE

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REFERENCES

1. Mitchell GF, Guo CY, Benjamin EJ, et al. Cross-sectional correlates of increased aortic stiffness in the community: the Framingham Heart Study. Circulation 2007;115:2628–2636.
2. Boutouyrie P, Tropeano AI, Asmar R, et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension 2002;39:10–15.
3. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001;37:1236–1241.
4. Laurent S, Katsahian S, Fassot C, et al. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke 2003;34:1203–1206.
5. Mattace-Raso FU, van der Cammen TJ, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006;113:657–663.
6. Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: how to move forward? Neurology 2009;72:368–374.
7. Pase MP, Herbert A, Grima NA, et al. Arterial stiffness as a cause of cognitive decline and dementia: a systematic review and meta-analysis. Intern Med J 2012;42:808–815.
8. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. J Appl Physiol 2008;105:1652–1660.
9. Rabkin SW, Jarvie G. Comparison of vascular stiffness in vascular dementia, Alzheimer dementia and cognitive impairment. Blood Press 2011;20:274–283.
10. Rabkin SW. Arterial stiffness: detection and consequences in cognitive impairment and dementia of the elderly. J Alzheimers Dis 2012;32:541–549.
11. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension 2005;46:200–204.
12. Mitchell GF, van Buchem MA, Sigurdsson S, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility–Reykjavik study. Brain 2011;134:3398–3407.
13. Iadecola C, Park L, Capone C. Threats to the mind: aging, amyloid, and hypertension. Stroke 2009;40:S40–S44.
14. Henskens LH, Kroon AA, van Oostenbrugge RJ, et al. Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. Hypertension 2008;52:1120–1126.
15. Kearney-Schwartz A, Rossignol P, Bracard S, et al. Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. Stroke 2009;40:1229–1236.
16. Poels MM, Zaccai K, Verwoert GC, et al. Arterial stiffness and cerebral small vessel disease: the Rotterdam Scan study. Stroke 2012;43:2637–2642.
17. Van Elderen SG, Brandts A, Westenberg JJ, et al. Aortic stiffness is associated with cardiac function and cerebral small vessel disease in patients with type 1 diabetes mellitus: assessment by magnetic resonance imaging. Eur Radiol 2010;20:1132–1138.
18. Rosano C, Watson N, Chang Y, et al. Aortic pulse wave velocity predicts focal white matter hyperintensities in a biracial cohort of older adults. Hypertension 2013;61:160–165.
19. Brisset M, Boutouyrie P, Pico F, et al. Large-vessel correlates of cerebral small-vessel disease. Neurology 2013;80:662–669.
20. Tsao CW, Seshadri S, Beiser AS, et al. Relations of arterial stiffness and endothelial function to brain aging in the community. Neurology 2013;81:984–991.
21. Brandts A, van Elderen SG, Westenberg JJ, et al. Association of aortic arch pulse wave velocity with left ventricular mass and lacunar brain infarcts in hypertensive patients: assessment with MR imaging. Radiology 2009;253:681–688.
22. Tarumi T, Shah F, Tanaka H, et al. Association between central elastic artery stiffness and cerebral perfusion in deep subcortical gray and white matter. Am J Hypertens 2011;24:1108–1113.
23. Geerlings MI, Appelman AP, Vincken KL, et al. Brain volumes and cerebrovascular lesions on MRI in patients with atherosclerotic disease: the SMART-MR study. Atherosclerosis 2010;210:130–136.
24. Muller M, Appelman AP, van der Graaf Y, et al. Brain atrophy and cognition: interaction with cerebrovascular pathology? Neurobiol Aging 2011;32:885–893.
25. Geerlings MI, Appelman AP, Vincken KL, et al. Association of white matter lesions and lacunar infarcts with executive functioning: the SMART-MR study. Am J Epidemiol 2009;170:1147–1155.
26. Simons PC, Algra A, Bots ML, et al. Common carotid intima-media thickness and arterial stiffness: indicators of cardiovascular risk in high-risk patients: the SMART Study (Second Manifestations of ARTerial disease). Circulation 1999;100:951–957.
27. Dijk JM, Algra A, van der Graaf Y, et al. Carotid stiffness and the risk of new vascular events in patients with manifest cardiovascular disease: the SMART study. Eur Heart J 2005;26:1213–1220.
28. Chirinos JA. Arterial stiffness: basic concepts and measurement techniques. J Cardiovasc Transl Res 2012;5:243–255.
29. Appelman AP, van der Graaf Y, Vincken KL, et al. Total cerebral blood flow, white matter lesions and brain atrophy: the SMART-MR study. J Cereb Blood Flow Metab 2008;28:633–639.
30. Anbeek P, Vincken KL, van Osch MJ, et al. Probabilistic segmentation of white matter lesions in MR imaging. Neuroimage 2004;21:1037–1044.
31. Anbeek P, Vincken KL, van Bochove GS, et al. Probabilistic segmentation of brain tissue in MR imaging. Neuroimage 2005;27:795–804.
32. Elgersma OEH, van Leersum M, Buijs PC, et al. Changes over time in optimal duplex threshold for the identification of patients eligible for carotid endarterectomy. Stroke 1998;29:2352–2356.

33. Donders AR, van der Heijden GJ, Stijnen T, et al. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087–1091.
34. Knol MJ, Le CS, Algra A, et al. Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. CMAJ 2012;184:895–899.
35. Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation 2004;109:III27–III32.
36. Hughes TM, Kuller LH, Barinas-Mitchell EJ, et al. Pulse wave velocity is associated with β-amyloid deposition in the brains of very elderly adults. Neurology 2013;81:1711–1718.
37. Cohn JN. Arterial stiffness, vascular disease, and risk of cardiovascular events. Circulation 2006;113:601–603.
38. Shahin Y, Khan JA, Chetter I. Angiotensin converting enzyme inhibitors effect on arterial stiffness and wave reflections: a meta-analysis and meta-regression of randomised controlled trials. Atherosclerosis 2012; 221:18–33.
39. Mattace-Raso FU, van der Cammen TJ, Sayed-Tabatabaei FA, et al. Angiotensin-converting enzyme gene polymorphism and common carotid stiffness: the Rotterdam study. Atherosclerosis 2004;174:121–126.
40. Vermeersch SJ, Rietzschel ER, De Buyzere ML, et al. Age and gender related patterns in carotid-femoral PWV and carotid and femoral stiffness in a large healthy, middle-aged population. J Hypertens 2008;26:1411–1419.

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