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# Arterial Stiffness, Cognitive Decline, and Risk of Dementia The Rotterdam Study

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**Background and Purpose**—Arterial stiffness is associated with an increased risk of myocardial infarction and stroke, independent of classical vascular risk factors. Vascular factors and stroke are associated with cognitive function and dementia. We examined whether arterial stiffness was independently associated with cognitive function and dementia.

**Methods**—The present study was based on the Rotterdam Study, a prospective population-based cohort study ongoing since 1990. During the third examination (1997–1999) arterial stiffness was measured by assessment of pulse wave velocity and carotid distensibility. Cognitive function was assessed during the third and fourth examination (2002–2004) with a neuropsychological test battery. We used linear and logistic regression to estimate the association of arterial stiffness with cognitive function and cognitive decline. From the third examination until January 1, 2005, we identified 156 incident dementia cases. Cox proportional hazard models were used to estimate the association between arterial stiffness and the risk of dementia.

**Results**—After adjustment for cardiovascular risk factors we found an association of increased pulse wave velocity with poorer performance on the Stroop test (adjusted  $\beta$ -coefficient [95% confidence interval] 1.13 [0.26 to 1.99] per standard deviation increase in pulse wave velocity) but not with performance on other cognitive tests. No associations were found between measures of arterial stiffness and cognitive decline or risk of dementia after adjustment for cardiovascular factors.

**Conclusions**—We did not identify arterial stiffness as an independent risk factor of cognitive decline or risk of dementia. (*Stroke*. 2007;38:888-892.)

**Key Words:** Alzheimer disease ■ dementia ■ risk factors ■ vascular disease

Arterial stiffness is a predictor of cardiovascular disease and mortality. Recently, the aortic pulse wave velocity index, a measure of arterial stiffness, was found to be of added value above traditional cardiovascular risk factors in the prediction of coronary heart disease and stroke.<sup>1</sup> Elevated arterial stiffness is a result of structural and functional changes of the vessel wall that occur with aging. Furthermore, higher arterial stiffness is associated with higher systolic blood pressure, increased pulse pressure, and atherosclerosis.<sup>2</sup>

Many studies have demonstrated an association of vascular factors and cerebrovascular disease with dementia and cognitive decline.<sup>3</sup> Recently, some studies reported an association between increased arterial stiffness, measured by pulse wave velocity (PWV), and poor cognitive function and suggested that arterial stiffness may be a determinant of cognitive decline and dementia.<sup>4–6</sup> However, these studies were all small, cross-sectional, and mostly performed in selected clinic-based samples. To date, no prospective studies have been reported that examined the association of arterial stiffness with cognitive decline or dementia.

In this study we set out to investigate the association between arterial stiffness and cognitive function, cognitive decline, and risk of dementia in the general population. Furthermore, to investigate whether arterial stiffness may be an independent risk factor of cognitive decline and dementia, we examined whether these associations were independent of cardiovascular factors.

## Methods

### Study Sample

This study was based on the Rotterdam Study, a prospective population-based cohort study among 7983 elderly subjects aged 55 years and older.<sup>7</sup> Baseline examinations were performed from 1990 through 1993. Participants were interviewed at their homes and subsequently examined at the research center. Follow-up examinations were conducted in 1993 to 1994, 1997 to 1999, and in 2002 to 2004. The Medical Ethics Committee of Erasmus Medical Center approved the study, and written informed consent was obtained from all participants. Arterial stiffness was first measured during the third survey in 1997 to 1999 in 3779 of the 4024 persons who visited the research center. Missing information on PWV or carotid distensibil-

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ity was almost entirely because of logistic reasons, particularly malfunctioning equipment or unavailability of technicians. Cognitive function was assessed at the third examination in 1997 to 1999 and the fourth examination in 2002 to 2004.

We excluded individuals with dementia at the time of the third examination, which left 3714 persons who had arterial stiffness measurements, underwent neuropsychological testing, and were not demented at the third examination to be included in our analyses. Follow-up for incident dementia was virtually complete until January 1, 2005. Of the 3714 persons, 947 persons did not visit the research center for the fourth examination. Of these, 527 persons had died and 420 persons refused to visit the center. As a result, the analyses regarding arterial stiffness and change in cognitive function were based on 2767 persons who underwent neuropsychological testing during 1997 to 1999 and 2002 to 2004.

## Measures of Arterial Stiffness

### PWV

Carotid–femoral PWV, a measure of aortic stiffness, was measured with persons in supine position. PWV was assessed with an automatic device (Complior; Artech Medica).<sup>8</sup> The time delay between the rapid upstroke of the feet of simultaneously recorded pulse waves in the carotid artery and the femoral artery was recorded. The distance between recording sites in the carotid and the femoral arteries (the carotid artery and the groin) was measured with a tape over the surface of the body. The ratio between the foot-to-foot delay and the distance covered by the pulse wave is the PWV and is expressed in meters per second.

### Carotid Distensibility

Carotid distensibility was measured at the right common carotid artery with the subjects in supine position and the head slightly tilted to the contra lateral side. The vessel wall motion was assessed with a duplex scanner (ATL Ultra mark IV, operation frequency 7.5 MHz) connected to a vessel wall movement detector system.<sup>9</sup> After 5 minutes of rest, a region at 1.5 cm proximal to the origin of the bulb of the artery was identified using B-mode ultrasound. The displacement of the arterial walls was obtained by processing the radio frequency signals originating from 2 selected sample volumes positioned over the anterior and posterior walls. The end-diastolic diameter (D), the absolute stroke change in diameter during systole ( $\Delta D$ ), and the relative stroke change in diameter ( $\Delta D/D$ ) were computed as the mean of 4 cardiac cycles of three successive recordings. Blood pressure was measured twice with a Dinamap automatic blood pressure recorder during the measurement session. The mean was taken as the person's reading. Pulse pressure ( $\Delta P$ ) was defined as the difference between systolic and diastolic blood pressure. The cross-sectional arterial wall distensibility coefficient was calculated according to the following equation: distensibility coefficient =  $2 (\Delta D/D)/\Delta P$  ( $10^{-3}$  kPa). In a reproducibility study performed among 47 subjects, the intraclass correlation coefficient was 0.80 for both the PWV and the carotid distensibility coefficient.

### Assessment of Cognitive Function

The Mini Mental State Examination (MMSE) is a widely used test for global cognitive function.<sup>10</sup> Executive cognitive function was measured with the Letter-Digit Substitution Task, an abbreviated Stroop Test and the Word Fluency Test. The Letter-Digit Substitution Task is a modified version of the Symbol Digit Modalities Test<sup>11</sup> and asks the participants to make as many letter–digit combinations as possible in 60 seconds. The abbreviated Stroop test consists of 3 subtasks in which the participant is shown a card with 40 items that have to be named.<sup>12</sup> The first card contains color names, printed in black; the second card contains colored blocks; the third card contains color names, printed in a different color than the color name. As an outcome we used time needed for the third trial in which the participants are asked to name the color in which the color name is printed. In the Word Fluency Test, used to test verbal fluency, participants were asked to name as many animals as possible within 60 seconds.

## Diagnosis of Dementia

The diagnosis of dementia was made after a 3-step protocol.<sup>13</sup> Two brief tests of cognition (MMSE and Geriatric Mental State schedule organic level) were used to screen all subjects. Screen-positives (MMSE score  $<26$  or Geriatric Mental State schedule organic level  $>0$ ) underwent the Cambridge examination for mental disorders of the elderly (Camdex). Subjects who were suspected of having dementia were examined by a neuropsychologist if additional neuropsychological testing was required for diagnosis. When available, imaging data were used. In addition, the total cohort was continuously monitored for incident dementia through computerized linkage between the study database and digitalized medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care. The diagnosis of dementia and subtypes of dementia was made in accordance with internationally accepted criteria for dementia, Alzheimer disease (AD) (NINCDS-ADRDA), and vascular dementia (NINDS-AIREN) by a panel of a neurologist, a neuropsychologist, and a research physician.

### Covariates

Level of education was obtained during the baseline interview and dichotomized into primary education or less and more than primary education. At the research center clinical measures were obtained. Systolic and diastolic blood pressures were measured twice on the right arm with a random-zero sphygmomanometer, after the participant had been seated for at least 5 minutes. The mean of the 2 blood pressure values was used in the analyses. Pulse pressure was defined as the difference between systolic and diastolic blood pressure. Mean arterial pressure was calculated as diastolic blood pressure plus one-third of the pulse pressure. The body mass index was calculated (weight [kg]/length [m]<sup>2</sup>). Fasting serum total and high-density lipoprotein cholesterol values were determined by an automated enzymatic procedure (Boehringer Mannheim System). Genotyping for *APOE* was performed on coded DNA specimens without knowledge of diagnosis. Persons were categorized on the basis of presence or absence of an *APOE*  $\epsilon 4$  allele. Persons with the *APOE*  $\epsilon 2/\epsilon 4$  genotype were excluded from the analyses. Furthermore, ultrasonography of both carotid arteries was performed. As an indicator of atherosclerosis of the carotid arteries we used intima-media thickness. Common carotid intima-media thickness was determined as the average of the maximum intima-media thickness of near-wall and far-wall measurements, and the average of left and right common carotid intima-media thickness was computed. Diabetes mellitus was defined as the use of blood glucose-lowering medication and/or fasting serum glucose level  $\geq 7.0$  mmol/L.

### Data Analysis

First, we examined the association of PWV and carotid distensibility per standard deviation (SD) increase with cognitive function by means of linear regression models, adjusted for age, sex, and education. Further adjustment was made for mean arterial pressure and heart rate as these measures have a direct effect on arterial stiffness. Then, to examine whether associations were independent of other vascular factors, we adjusted for body mass index, smoking, intima-media thickness, total cholesterol, high-density lipoprotein cholesterol, and diabetes mellitus.

Next, we examined the association between arterial stiffness and cognitive decline with logistic regression models. Decline on cognitive tests was defined as a negative difference between the test scores from the third and fourth examination  $>1$  SD of the mean difference. Analyses were adjusted as described for the cross-sectional analyses. Because stroke has been related to cognition and an association has been reported between arterial stiffness and risk of stroke,<sup>1</sup> we adjusted for prevalent and incident strokes in additional analyses. To assess whether associations differed across age categories we repeated the analyses in strata of age ( $\leq 75$  years and  $>75$  years). We repeated the analyses adjusting for cognitive function at baseline. Also, analyses were repeated excluding 89 persons of the 2767 persons included in the population for analyses regarding change in cognitive function who had become demented during follow-up.

**TABLE 1. Baseline Characteristics of the Study Population, Persons Who Participated in the Third Examination (n=3714), Persons Who Participated in the Third Examination but Not in the Fourth Examination (n=947), and Persons Who Participated in Both Examinations (n=2767)**

	Third Examination, n=3714	Third but not Fourth Examination, n=947	Third and Fourth Examination, n=2767
Men, %	42.3	43.6	41.9
Age, years (SD)	72.0 (6.7)	75.7 (7.3)	70.7 (6.0)
Primary education, %	29.0	34.9	27.0
Prevalent stroke cases, %	3.8	7.0	2.7
PWV, m/s (SD)	13.5 (3.0)	14.5 (3.3)	13.2 (2.9)*
Distensibility coefficient (10 <sup>-3</sup> kPa (SD)	10.5 (4.4)	9.2 (4.2)	10.9 (4.3)
Mean arterial Pressure, mm Hg (SD)	106.7 (12.8)	108.2 (13.7)	106.1 (12.5)*
Heart rate, bpm (SD)	75.2 (14.6)	77.2 (15.4)	74.5 (14.2)*
Diabetes mellitus, %	10.9	16.3	9.0*
Body mass index, kg/m <sup>2</sup> (SD)	26.8 (4.0)	26.7 (4.1)	26.9 (3.9)
Current smokers, %	16.0	18.8	15.1*
Total cholesterol, mmol/L (SD)	5.8 (1.0)	5.8 (1.0)	5.9 (1.0)
High-density lipoprotein cholesterol, mmol/L (SD)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)*
Intima-media thickness, mm (SD)	0.9 (0.2)	0.9 (0.2)	0.9 (0.1)*
Mini Mental State Examination (SD)	27.7 (2.0)	26.9 (2.6)	28.0 (1.6)*
Word Fluency Test, no. of correct answers (SD)	20.9 (5.5)	19.0 (5.5)	21.5 (5.3)*
Stroop Test, seconds (SD)	57.2 (21.1)	66.0 (27.2)	54.4 (17.8)*
Letter Digit Substitution Test, no. of correct answers (SD)	26.6 (7.1)	23.4 (7.5)	27.7 (6.6)*

\*Age and sex adjusted difference between the groups <0.05.

Finally, we used Cox proportional hazard models to examine the association between arterial stiffness and the risk of dementia and subtypes of dementia. Follow-up time was defined as the time of arterial stiffness measurement until dementia diagnosis, death, or end of study, whichever came first. We examined the association of PWV and carotid distensibility with dementia per SD increase of PWV and carotid distensibility. We adjusted for age, sex, and education, and subsequently for mean arterial pressure, heart rate, and cardiovascular risk factors. To investigate whether *APOE* genotype modified the association of PWV and carotid distensibility with dementia, we examined the association in strata of carriers and noncarriers of the *APOE*  $\epsilon$ 4 allele and computed interaction terms between measures of arterial stiffness and the *APOE* genotype.

All analyses were performed using the statistical package SPSS 11.0 for Windows (SPSS Inc).

## Results

Characteristics of persons who visited the center during the third and fourth examination are shown in Table 1. Persons

who participated in both the third and the fourth examination had a better cardiovascular risk profile and performed better on all cognitive tests compared with persons who only participated in the third examination also when differences in age were taken into account. PWV and carotid distensibility were normally distributed and inversely correlated (Spearman correlation coefficient,  $-0.41$ ;  $P<0.001$ ).

After adjustment for age, sex, and education, statistically significant associations were found for increased PWV and worse performance on the MMSE, the Stroop Test, and the Word Fluency Test, and for decreased carotid distensibility and worse performance on the MMSE and the Stroop Test (model 1 in Table 2).

Adjustments for mean arterial pressure and heart rate attenuated all associations. The associations were attenuated further after adjusting for cardiovascular factors and only the association

**TABLE 2. Association of Arterial Stiffness as Measured Through PWV and CD With Cognitive Function Using Linear Regression Models**

	Model 1 Difference in Test Scores (95% CI)				Model 2 Difference in Test Scores (95% CI)			
	MMSE	Letter-Digit Substitution Test	Stroop Test	Word Fluency Test	MMSE	Letter-Digit	Stroop Test	Word Fluency Test
PWV per SD	-0.08 (-0.15; -0.01)	-0.19 (-0.42; 0.05)	1.39 (0.65; 2.13)	-0.31 (-0.50; -0.12)	-0.05 (-0.13; 0.03)	-0.08 (-0.36; 0.19)	1.13 (0.26; 1.99)	-0.18 (-0.41; 0.05)
CD per SD	0.09 (0.01; 0.16)	0.12 (-0.13; 0.36)	-0.82 (-1.56; -0.08)	0.14 (-0.06; 0.35)	0.04 (-0.06; 0.13)	-0.04 (-0.34; 0.26)	-0.30 (-1.20; 0.61)	-0.08 (-0.34; 0.17)

Model 1 adjusted for age, sex, and education.

Model 2 additionally adjusted for mean arterial pressure, heart rate, current smoking, diabetes mellitus, body mass index, total cholesterol, high-density lipid cholesterol, and intima media thickness.

CD indicates carotid distensibility.

**TABLE 3. Association Between Arterial Stiffness and Cognitive Decline**

	Model 1 OR for Decline (95% CI)				Model 2 OR for Decline (95% CI)			
	MMSE	Letter-Digit Substitution Test	Stroop Test	Word Fluency Test	MMSE	Letter-Digit Substitution Test	Stroop Test	Word Fluency Test
PWV per SD	0.98 (0.86–1.12)	1.14 (1.00–1.31)	1.00 (0.85–1.17)	1.07 (0.95–1.21)	0.93 (0.79–1.09)	1.09 (0.92–1.28)	0.89 (0.73–1.08)	1.07 (0.93–1.23)
CD per SD	0.94 (0.81–1.09)	0.90 (0.78–1.04)	0.99 (0.83–1.18)	0.91 (0.80–1.03)	0.99 (0.82–1.19)	0.89 (0.75–1.07)	1.10 (0.89–1.37)	0.97 (0.84–1.13)

Model 1 adjusted for age, sex, and education.

Model 2 additionally adjusted for mean arterial pressure, heart rate, current smoking, diabetes mellitus, body mass index, total cholesterol, high-density lipid cholesterol, and intima-media thickness.

OR indicates odds ratio.

between PWV and worse performance on the Stroop Test remained statistically significant (model 2 in Table 2).

No association was found between arterial stiffness and cognitive decline (models 1 and 2 in Table 3). The incidence rate of stroke in the Rotterdam Study was 9.4 per 1000 person-years.<sup>14</sup> Additional adjustment for prevalent and incident stroke did not change the associations. The associations were similar for younger and older people ( $\leq 75$  years,  $> 75$  years). Associations did not change after adjusting for baseline cognitive function and after exclusion of persons who had become demented.

The incidence rate of dementia in the Rotterdam Study was 9.8 per 1000 person-years.<sup>15</sup> During a mean (SD) follow-up of 4.4 (0.9) years, we identified 156 persons with incident dementia (including 89 persons who visited the research center during the fourth survey and 67 patients who were identified through medical records), of whom 136 persons had AD diagnosed and 11 persons had vascular dementia diagnosed.

Table 4 shows that PWV and carotid distensibility were not associated with risk of dementia. For AD, the hazard ratio (95% CI) was 0.90 (0.75 to 1.07) per SD increase in PWV. For vascular dementia, there seemed to be an association (hazard ratio [95% CI] 1.47 [0.94 to 2.30]) per SD increase in PWV, although this was not significant, possibly because of the low number of vascular dementia cases. Per SD increase in carotid distensibility, the hazard ratio (95% CI) for AD was 1.14 (0.91 to 1.43) and 0.58 (0.21 to 1.57) for vascular dementia. The associations did not differ between carriers and noncarriers of the *APOE*  $\epsilon 4$  allele (probability value of the interaction term between PWV and *APOE* genotype was 0.89 and 0.94 between carotid distensibility and *APOE* genotype).

**Discussion**

We did not find an association between arterial stiffness and cognitive decline or the risk of dementia. Although we found

associations between arterial stiffness and several domains of cognitive function in cross-sectional analyses, these associations were small and after adjustment for mean arterial pressure, heart rate, and cardiovascular risk factors, only the association between increased PWV and poor performance on the Stroop Test remained.

Some aspects of the present study need to be discussed. Strengths of the Rotterdam Study are its population-based setting, its large number of persons, and its virtually complete follow-up.

A limitation of the study is that because information on cognitive decline was only available for persons who participated in both the third and the fourth examination, selective attrition may have affected the results of our analyses regarding change in cognitive function. Persons included in these analyses were younger and had a better cardiovascular risk profile (including measures of arterial stiffness) than persons who did not participate in the fourth examination. Because age and cardiovascular factors are associated with cognitive function, this may have affected our power to find an association with cognitive decline. Another limitation is that the results of the analyses regarding cognitive decline may have been affected by regression to the mean. Regression to the mean may result in an underestimation of the association. However, follow-up was complete for the outcome dementia and we also found no relation between arterial stiffness and risk of dementia.

Few studies have examined the association between arterial stiffness and cognition.

Recently, an association, independent of cardiovascular factors, between increased PWV and impaired cognitive function, defined by MMSE score, was found in patients who were referred to a memory clinic<sup>6</sup> and in community-dwelling elderly.<sup>4</sup> Our finding of an association independent of cardio-

**TABLE 4. Association Between Arterial Stiffness and Risk of Dementia**

	PWV HR (95% CI)		CD HR (95% CI)	
	Model 1	Model 2	Model 1	Model 2
Per SD increase	0.97 (0.82–1.15)	0.91 (0.75–1.10)	1.08 (0.88–1.34)	1.05 (0.81–1.35)

Model 1 adjusted for age, sex, and education.

Model 2 additionally adjusted for mean arterial pressure, heart rate, current smoking, diabetes mellitus, body mass index, total cholesterol, high-density lipid cholesterol, and intima-media thickness.

HR indicates hazard ratio.

vascular factors between increased PWV and worse performance on the Stroop Test is in line with the notion that arterial stiffness affects cognitive function. However, we did not find independent associations between increased arterial stiffness and other cognitive tests. This may be explained by more extensive adjustments in our study compared with previous studies, including adjustments for carotid intima-media thickness, an indicator of atherosclerosis, body mass index, pulse rate, and mean arterial pressure.

Few studies examined the association between arterial stiffness and dementia. In one study 308 elderly with symptoms of memory loss were evaluated and classified in 4 groups (AD, vascular dementia, mild cognitive impairment, and normal cognitive function).<sup>5</sup> Persons with vascular dementia, AD, and mild cognitive impairment had a higher PWV than those without cognitive impairment after adjustments for age, sex, systolic blood pressure, antihypertensive treatment, and presence of cardiovascular diseases. In another study brachial-ankle PWV was compared between patients with AD, vascular dementia, and cognitively normal age-matched controls. Arterial stiffness was higher in patients with vascular dementia than in those with AD or those without dementia.<sup>16</sup> Another study reported an inverse correlation, adjusted for age, sex, mean arterial pressure, and antihypertensive treatment, between heart-brachial PWV and cognitive function, measured by the Hasegawa Dementia Scale Revised, in nonvascular dementia patients and persons with mild cognitive impairment.<sup>17</sup>

In our prospective study, we did not find an association between arterial stiffness and risk of dementia or cognitive decline. However, we cannot completely rule out an association between increased arterial stiffness and risk of vascular dementia because of the low number of incident vascular dementia cases.

Arterial stiffness is strongly associated with hypertension and atherosclerosis that have both been related to an increased risk of dementia.<sup>2,18–20</sup> Therefore, an association of increased arterial stiffness with cognitive decline and dementia seemed plausible. Mechanisms for such an association include cerebrovascular disease (for instance, lacunar infarction or white matter lesions) and cerebral hypoperfusion. Though previous studies suggested that arterial stiffness might provide additional value above other cardiovascular risk factors in relation to cognitive decline or dementia, our data do not support this hypothesis.

To conclude, we did not identify arterial stiffness as an independent risk factor of cognitive decline or risk of dementia.

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### Disclosures

None.

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