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Atherosclerotic calcification is related to a higher risk of dementia and cognitive decline

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Abstract

Background: Longitudinal data on the role of atherosclerosis in different vessel beds in the etiology of cognitive impairment and dementia are scarce and inconsistent.
Methods: Between 2003–2006, 2364 nondemented persons underwent computed tomography of the coronaries, aortic arch, extracranial, and intracranial carotid arteries to quantify atherosclerotic calcification. Participants were followed for incident dementia (n = 90) until April 2012. At baseline and follow-up participants also underwent a cognitive test battery.
Results: Larger calcification volume in all vessels, except in the coronaries, was associated with a higher risk of dementia. After adjustment for relevant confounders, extracranial carotid artery calcification remained significantly associated with a higher risk of dementia [hazard ratio per standard deviation increase in calcification volume: 1.37 (1.05, 1.79)]. Additional analyses for Alzheimer's disease only or censoring for stroke showed similar results. Larger calcification volumes were also associated with cognitive decline.
Conclusions: Atherosclerosis, in particular in the extracranial carotid arteries, is related to a higher risk of dementia and cognitive decline.

Keywords: Atherosclerosis; Arterial calcification; Epidemiology; Imaging; Dementia; Cognitive decline

1. Introduction

Dementia, including Alzheimer's disease, is a devastating condition with a huge societal impact, both in terms of patient suffering and financial cost [1,2]. An important feature of dementia is the long preclinical phase, during which subtle cognitive deficits develop that can only be measured using dedicated neuropsychological tests [3]. The underlying etiology of dementia and cognitive decline is multifactorial and involves different pathologies which interact and accumulate over the course of years [4]. In addition to beta-amyloid and tau pathology, the role of vascular pathology in the etiology of dementia and Alzheimer's disease is increasingly being recognized [5,6].

Atherosclerosis is highly frequent in the aging population and is considered the most important hallmark of vascular pathology [7]. Thus far, most studies have focused on atherosclerosis in the carotid bifurcation in relation to dementia [8–10]. Indeed, both carotid intima-media thickness and carotid plaques have been associated with dementia, including Alzheimer's disease [8–10].

However, several important questions remain unanswered. First, atherosclerosis is a systemic disease, but its burden differs considerably across vessel beds [7,11,12]. It is therefore conceivable that the contribution of atherosclerosis to dementia may vary depending on the vessel bed. Such differential contribution of atherosclerosis in various vessel beds to disease risk has already been demonstrated for stroke, and even for mortality [13,14]. Second, the study of vascular factors in dementia is often complicated by stroke, which can act as intermediate factor [9,10]. It is therefore

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important to also investigate the role of atherosclerosis in dementia independent from stroke. Finally, given that both atherosclerosis and dementia develop over the course of years, it is important to study how atherosclerosis affects the preclinical phase of dementia, namely the period of cognitive decline without overt clinical disease.

Disentangling the exact role of atherosclerosis in dementia is important, because this knowledge may then serve as basis to develop opportunities for therapeutic or preventive intervention. Against this background, we aimed to study the relationship of atherosclerosis in the coronary arteries, aortic arch, extracranial and intracranial internal carotid arteries with incident dementia, including Alzheimer's disease and the potential influence of stroke on these associations. Finally, we focused on the relationship of atherosclerosis with cognitive decline.

2. Methods

2.1. Setting

This study is based on the Rotterdam Study, a prospective, population-based study aimed at investigating determinants of chronic diseases in the elderly [15]. The original cohort comprised 7983 participants aged 55 years or older and was extended in 2000–2001 with 3011 persons. At study entry and every 3–4 years, all participants are re-examined in a dedicated research center.

Between 2003 and 2006, all participants visiting the research center were invited to undergo non-enhanced computed tomography (CT). Therefore for this study, 2003–2006 is taken as baseline. In total, we scanned 2524 participants (response rate 78%). Both during the 2003–2006-visit and the following visit in 2008–2012 persons underwent cognitive testing. The cohort was screened for dementia at baseline to exclude persons with prevalent dementia. From then onwards, the dementia-free cohort was followed-up for dementia through in-person screening at the follow-up visit and through continuous monitoring for dementia via computerized linkage between the study database and medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care, from baseline until April 27, 2012. The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants.

2.2. Sample for analysis

Fig. 1 shows the composition of the study population. Due to the presence of a pacemaker, coronary stent implantations or image artifacts, 111 examinations from the 2524 were not gradable, leaving a total of 2413 participants with a complete CT examination. From these, 2364 participants were at risk for developing dementia (incorrect dementia-screening or prevalent dementia excluded), encompassing the study population at baseline.

From these 2364 participants, 437 refused a second cognitive examination or had died during follow-up, 38 were incapable of follow-up visit (e.g. physical limitations), 16 had been institutionalized or moved, 10 could not be reached, for seven participants the appointment was postponed for logistical reasons, and in nine participants the cognitive assessment was incomplete and could not be used. This left 1847 participants with data on cognitive change (Mini-Mental State Examination, MMSE, or at least one cognitive test).

2.3. CT Acquisition and processing

We used a 16-slice (n = 785) or 64-slice (n = 1739) multidetector CT scanner (Somatom Sensation 16 or 64, Siemens, Forchheim, Germany) to perform noncontrast CT-scanning. Using a cardiac scan and a scan that reached from the aortic arch to the intracranial vasculature (1 cm above the sella turcica), we scanned the following vessel beds: the coronary arteries, the aortic arch, the extracranial carotid arteries, and the intracranial carotid arteries (Fig. 2). Detailed information regarding imaging parameters of both scans is described elsewhere [12].

We used dedicated commercially available software (Syngo Calcium Scoring, Siemens, Germany) to quantify calcification volume in the coronary arteries, aortic arch, and extracranial carotid arteries [12]. For calcification in the intracranial carotid arteries we used a semiautomated scoring method which is described in detail elsewhere [16]. Briefly, we delineated calcification in the intracranial carotid arteries manually in every CT slice. Next, we calculated the volume of intracranial carotid artery calcification by multiplying the number of pixels above the threshold of 130 Hounsfield units [17] with the pixel size and slice increment.

The interrater reliability of this method is very good (intraclass correlation coefficient, 0.99) [16]. Calcification volumes in each vessel bed are expressed in cubic millimeters. Correlations between calcification across the four vessel beds ranged from 0.5 to 0.6 [12,18].

2.4. Ascertainment of dementia

We screened participants for dementia at baseline and follow-up using a three-step protocol [19,20]. The first screening step consisted of the MMSE and the Geriatric Mental Schedule (GMS) organic level. If participants were screen-positive (MMSE $<$ 26 or GMS organic level $>$ 0), they entered the second step which consisted of the Cambridge Examination for Mental Disorders in the Elderly [20]. Additionally, persons underwent history taking, assessment of activities of daily living, informant interview, retrieval of relevant medical records, and additional neuropsychological testing. When information on neuroimaging was available (38/90 dementia cases; 42%), it was

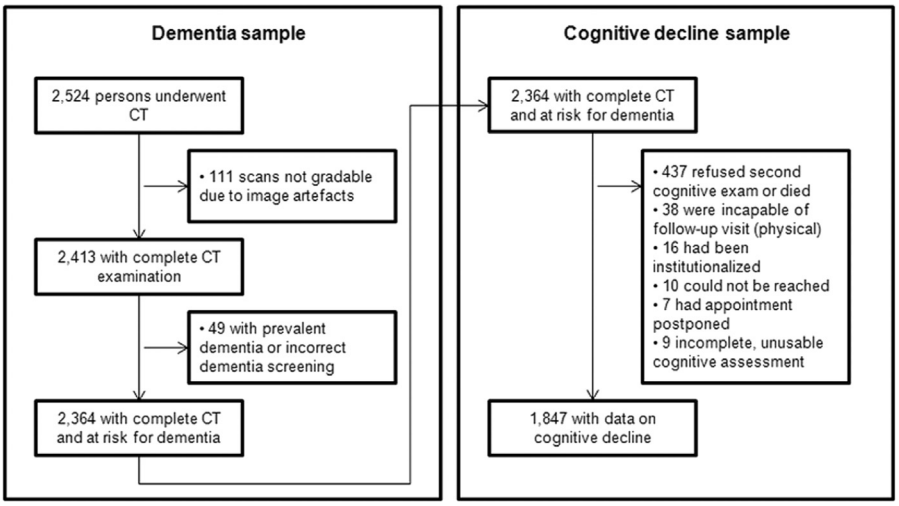

Fig. 1. Flowchart of the composition of the study sample.

used for decision making on the diagnosis. If sufficient information was already obtained through the medical records, neuropsychological testing was not performed. Third, all remaining cases were discussed in a consensus panel consisting of research physicians led by an experienced neurologist, deciding on the final diagnosis in accordance with standard criteria using the *Diagnostic and Statistical Manual of Mental Disorders, version III, revised (DSM-III-R)* criteria for dementia. If applicable, subtyping of dementia was done using the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for Alzheimer's disease and National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) for vascular dementia [21,22].

Additionally, the total cohort was continuously monitored for dementia through computerized linkage between the study database and medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care. This was important to identify those persons that became demented, who did not visit our research center and therefore were not detected by our dementia screening. If available, the consensus panel used results from screening and information obtained by monitoring medical records to assess a dementia diagnosis. Consequently, in certain cases (18 out of 90 cases) information from both sources was used. For the remaining cases, 53 were detected trough computerized linkage and 19 through return visits.

2.5. Assessment of cognitive function and cognitive decline

Both at baseline and at a follow-up examination in 2008–2012, participants underwent the MMSE [23]. In addition, each participant underwent a more extensive neuropsychological test battery which consisted of the following tests: the Stroop test (reading, color-naming, and interference subtask), the Letter-Digit Substitution Task (LDST), a Word-Fluency test (WFT), and a 15-Word verbal Learning Task (15-WLT) [24,25]. We calculated decline for MMSE and each cognitive test by subtracting the test-score at follow-up from the test-score at baseline for each individual. The differences for cognitive tests were subsequently standardized (i.e. Z-scores) to aid the comparison across tests. Z-scores for each subtask of the Stroop test were inverted, because higher scores for these indicate worse performance, whereas higher scores on the other tests indicate better performance. Finally, we averaged the Z-scores to yield a measure of global cognition.

2.6. Other measurements in the Rotterdam Study

We collected detailed information on cardiovascular risk factors by interview, physical examination and blood sampling [15]. The following cardiovascular risk factors were measured: obesity, hypertension, diabetes, hypercholesterolemia, low high-density lipoprotein (HDL)-cholesterol level, and smoking status. Obesity was defined as a body-mass index $\geq$ 30 kg/m^2. Hypertension was defined as systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg and/or the use of blood pressure lowering medication [26]. Diabetes was defined as fasting serum glucose levels $\geq$7.0 mmol/l and/or the use of antidiabetic therapy [27]. Hypercholesterolemia was defined as total cholesterol concentration $\geq$6.2 mmol/l and/or the use of lipid-lowering medication [28]. We defined low HDL-cholesterol as HDL-cholesterol $<$ 1.0 mmol/l [28]. Smoking was categorized into never or ever smoked. Level of education was assessed by self-report [25]. We performed apolipoprotein (*APOE*) - genotyping on coded genomic DNA samples and coded it positive (carrier of one or two ε4-alleles) or negative (noncarrier). The definition of stroke was based on World Health Organization criteria as a syndrome of rapidly developing symptoms of cerebral dysfunction lasting 24 hours or longer or leading to death, with apparent vascular cause [29,30]. History of stroke was

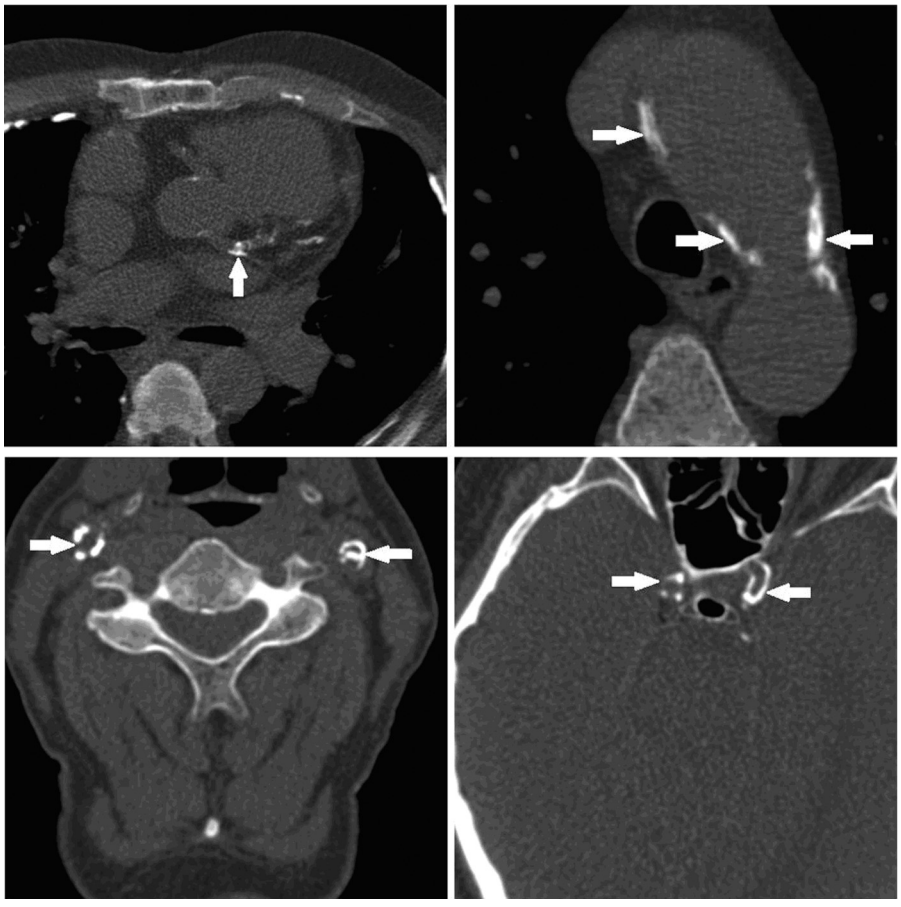

Fig. 2. Examples of calcification in the four examined vessel beds. Arrows indicate atherosclerotic calcified lesions in: the left coronary artery (upper left), the aortic arch (upper right), the left and the right extracranial internal carotid arteries (lower left), and the left and right intracranial internal carotid arteries (lower right).

assessed during the baseline interview and verified by reviewing medical records [29]. After enrolment, we continuously monitored participants for incident stroke through linkage of the study database with files from general practitioners. We also checked nursing home physicians' files and files from general practitioners of participants who moved out of the district. From the 152 stroke-cases in our study, neuroimaging was available in 101 persons (66 %). When neuroimaging was not available, strokes were categorized as "unspecified", but still considered as an event. Potential strokes were reviewed by research physicians and verified by an experienced stroke neurologist [29].

2.7. Statistical analysis

Because calcification volume had a skewed, non-normal distribution, we used natural log-transformed values and added 1.0 mm^3 to the nontransformed values to deal with calcium scores of zero [Ln(calcification + 1.0 mm^3)].

We assessed the relationship between calcification volume in each vessel bed and the risk of dementia using Cox regression models. In the first model we adjusted for age, sex and educational level (model 1). In a second model, we adjusted for cardiovascular risk factors (obesity, hypertension, diabetes mellitus, hypercholesterolemia, low HDL-cholesterol levels, and smoking status) and *APOE* ε4-carriership status (model 2). Next, associations between calcification and dementia were reanalyzed after exclusion of participants with prevalent stroke at baseline (n = 78) or incident stroke during the dementia follow-up (n = 74).

We used linear regression to study the relationship of calcification volume with decline in MMSE, global cognition and the standardized separate neurocognitive tests. The adjustments we performed were identical to those in models 1 and 2 used for dementia, with the addition of time interval between baseline and follow-up as covariate. Subsequent analyses were performed after exclusion of persons with stroke (n = 90) and dementia (n = 42).

IBM SPSS Statistics version 20 (International Business Machines Corporation, Armonk, NY) was used for statistical analyses.

3. Results

The baseline characteristics of our study participants are summarized in Table 1. (Supplementary Table 1 also depicts the characteristics of the source population, from which the current sample was derived.) The mean age at baseline was

Table 1
Baseline characteristics of the study population

Sample size	2364
Women	52.3%
Age, yrs	69.4 (6.7)
Highest education attained:	
Primary education	10.3%
Low level vocational training	20.8%
Medium level secondary training	17.9%
Medium level vocational to university training	49.1%
Obesity	23.9%
BMI, kg/m^2	27.7 (3.9)
Hypertension	73.7%
Systolic blood pressure, mmHg	146.7 (20.1)
Diastolic blood pressure, mmHg	80.3 (10.7)
Diabetes	11.2%
Serum glucose, mmol/L	5.7 (1.3)
Hypercholesterolemia	48.6%
Serum total cholesterol, mmol/L	5.7 (1.0)
Low HDL cholesterol	10.6%
Serum HDL cholesterol, mmol/L	1.4 (0.4)
Smoking, ever	67.5%
APOE ε4-carriers	25.6%

Abbreviations: *APOE*, apolipoprotein; BMI, body mass index; HDL, high density lipoprotein; n, number of cases; N, number of persons at risk; HR, hazard ratio; CI, confidence interval; SD, standard deviation.

NOTE. Values are means (standard deviation) for continuous variables and percentages for dichotomous variables.

69.4 ± 6.7 years and 52.3% of the participants were female. During 13,397 person years of follow-up, 90 participants developed dementia (incidence rate of 6.7 cases per 1000 person years). Of these, 73 were diagnosed with Alzheimer's disease, three with vascular dementia and 14 with other/undetermined types of dementia. In total, 152 participants suffered a stroke of whom 13 later developed dementia. Hence, 77 participants developed dementia without previous stroke (63 with Alzheimer's disease). On average, people declined 0.27 ± 2.00 points on the MMSE during a mean follow-up period of 6.0 ± 0.5 years.

We found that larger calcification volumes in the aortic arch, extracranial carotid arteries and intracranial carotid arteries, but not in the coronary arteries, were related to a higher risk of dementia (Table 2, model 1). Additional adjustment for cardiovascular risk factors and *APOE* ε4 status did slightly attenuate these associations (Table 2, model 2). We found similar associations for Alzheimer's disease (Table 2).

After censoring for stroke, both extracranial and intracranial carotid artery calcification remained statistically significantly associated with dementia [hazard ratio (HR) per standard deviation increase in calcification volume: 1.32 (95% confidence interval, CI: 1.02, 1.71) and 1.34 (95% CI: 1.01, 1.78), respectively]. Effect sizes for the remaining associations also remained similar, though statistically nonsignificant (Table 3).

For cognitive decline, we found that calcification in all vessel beds, including the coronary arteries, was associated with decline in global cognition and, apart from extracranial carotid artery calcification, with decline in MMSE (Table 4, model 1). Additional adjustment for cardiovascular risk factors and *APOE* ε4 status attenuated most associations, but the associations of coronary artery calcification with MMSE and the association of intracranial carotid artery calcification with MMSE and global cognition remained statistically significant [MMSE per SD increase—coronary artery calcification β= −0.15 (95% CI: −0.25, −0.05); intracranial carotid artery calcification β = −0.12 (95% CI: −0.22, −0.01)] [global cognition per SD increase: intracranial carotid artery calcification β= −0.03 (95% CI:−0.06, 0.00)] (Table 4, model 2). After censoring for stroke, coronary artery calcification remained statistically significantly associated with MMSE [MMSE per SD increase: coronary artery calcification β = −0.11 (95% CI: 0.21, −0.01)]. Effect sizes for

Table 2
Atherosclerotic calcification and the risk of dementia and Alzheimer's disease

	Dementia		Alzheimer's disease	
	n/N = 90/2364		n/N = 73/2364	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Per SD increase in:				
Model 1				
Coronary calcification	1.10 (0.86; 1.41)	.44	1.16 (0.88; 1.53)	.31
Aortic arch calcification	1.38 (1.02; 1.86)	.04	1.46 (1.04; 2.06)	.03
Extracranial carotid calcification	1.39 (1.09; 1.77)	<.01	1.31 (1.01; 1.72)	.05
Intracranial carotid calcification	1.31 (1.01; 1.70)	.05	1.29 (0.96; 1.74)	.09
Model 2				
Coronary calcification	1.12 (0.85; 1.48)	.43	1.17 (0.85; 1.60)	.34
Aortic arch calcification	1.27 (0.93; 1.73)	.13	1.32 (0.93; 1.89)	.12
Extracranial carotid calcification	1.37 (1.05; 1.79)	.02	1.26 (0.94; 1.68)	.13
Intracranial carotid calcification	1.32 (0.98; 1.77)	.07	1.22 (0.88; 1.70)	.23

Abbreviations: n, number of cases; N, number of persons at risk; HR, hazard ratio; CI, confidence interval; SD, standard deviation.

NOTE. Model 1: Adjusted for age, sex, and level of education. Model 2: As model 1, additionally adjusted for obesity, hypertension, diabetes mellitus, hypercholesterolemia, low HDL-cholesterol levels, smoking status and *APOE* ε4-carrier status.

Table 3
Atherosclerotic calcification and the risk of dementia and Alzheimer's disease, censored for stroke

	Dementia		Alzheimer's disease	
	n/N = 77/2212		n/N = 63/2212	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Per SD increase in:				
Coronary calcification	1.05 (0.80; 1.36)	.74	1.09 (0.81; 1.46)	.57
Aortic arch calcification	1.34 (0.97; 1.83)	.07	1.32 (0.92; 1.88)	.13
Extracranial carotid calcification	1.32 (1.02; 1.71)	.04	1.24 (0.94; 1.65)	.13
Intracranial carotid calcification	1.34 (1.01; 1.78)	.05	1.28 (0.93; 1.76)	.12

Abbreviations: n, number of cases; N, number of persons at risk; HR, hazard ratio; CI, confidence interval; SD, standard deviation.

NOTE. Adjusted for age, sex, and level of education.

Table 4
Calcification in different vessel beds and global cognitive decline

	Global cognition		MMSE	
	Difference in Z-score (95% CI)	*P*	Difference in points (95% CI)	*P*
Per SD increase in:				
Model 1				
Coronary calcification	−0.03 (−0.06; 0.00)	.03	−0.15 (−0.25; −0.05)	<.01
Aortic arch calcification	−0.03 (−0.05; 0.00)	.06	−0.11 (−0.21; −0.01)	.03
Extracranial carotid calcification	−0.03 (−0.06; 0.00)	.04	−0.07 (−0.16; 0.03)	.19
Intracranial carotid calcification	−0.04 (−0.07;−0.02)	<.01	−0.09 (−0.19; 0.00)	.06
Model 2				
Coronary calcification	−0.02 (−0.05; 0.01)	.13	−0.16 (−0.27; −0.05)	<.01
Aortic arch calcification	−0.01 (−0.04; 0.02)	.39	−0.11 (−0.22; −0.01)	.03
Extracranial carotid calcification	−0.02 (−0.05; 0.01)	.22	−0.07 (−0.17; 0.04)	.22
Intracranial carotid calcification	−0.03 (−0.06; 0.00)	.03	−0.12 (−0.22; −0.01)	.03

Abbreviations: HDL, high density lipoprotein; CI, confidence interval; SD, standard deviation.
NOTE. Model 1: Adjusted for age, sex, time interval, and level of education. Model 2: As model 1, additionally adjusted for obesity, hypertension, diabetes mellitus, hypercholesterolemia, low HDL-cholesterol levels, smoking status, and *APOE* ε4-carrier status.

the remaining associations were no longer statistically significant (Supplementary Table 2). After we excluded all persons who developed dementia during follow-up, we still found similar associations of calcification with cognitive decline (Supplementary Table 2).

Associations of calcification with the separate cognitive tests are shown in (Tables 5 and 6). We found most prominent associations of calcification volume in the coronary arteries and the intracranial carotid arteries with decline in scores on the LDST.

4. Discussion

In this sample of community-dwelling middle-aged and elderly persons, we found that atherosclerotic calcification, in particular in the extracranial carotid arteries, was related to a higher risk of dementia, including Alzheimer's disease. Furthermore, we found atherosclerotic calcification to be associated with cognitive decline in nondemented persons.

Strengths of our study include the longitudinal population-based setting, the image-based quantification of atherosclerosis, and the focus on both cognitive decline and dementia. Moreover, our close collaborations with general practitioners in the study area, in combination with the structure of the Dutch health care system allowed us to accomplish virtually complete follow-up with regard to development of dementia. The incidence rate of dementia in our sample was comparable to incidence rates reported in other studies [20,31].

Several potential limitations should also be addressed. First, additional adjustment for covariates affected the results regarding dementia and cognitive decline. Yet, in most cases the effect estimates remained largely unchanged. It is possible that addition of multiple covariates to the model in combination with the relatively small sample size may have led to less statistical power. Importantly, this does not necessarily imply that there is no real association between atherosclerosis and the outcomes. Second, we

Table 5
Calcification in different vessel beds and cognitive decline per single test (Stroop Test and LDST)

	Stroop reading*		Stroop naming*		Stroop CWI*		LDST	
	Difference in Z-score (95% CI)	*P*	Difference in Z-score (95% CI)	*P*	Difference in Z-score (95% CI)	*P*	Difference in Z-score (95% CI)	*P*
Per SD increase in:								
Model 1								
Coronary calcification	0.01 (−0.05; 0.07)	.72	0.02 (−0.03; 0.08)	.43	−0.01 (−0.06; 0.05)	.79	−0.06 (−0.12; −0.01)	.02
Aortic arch calcification	−0.02 (−0.08; 0.03)	.38	−0.00 (−0.05; 0.05)	.97	−0.01 (−0.07; 0.04)	.65	−0.06 (−0.11; 0.00)	.04
Extracranial carotid calcification	−0.01 (−0.06; 0.05)	.79	−0.02 (−0.07; 0.03)	.47	0.01 (−0.04; 0.07)	.67	−0.06 (−0.11;−0.01)	.02
Intracranial carotid calcification	−0.02 (−0.07; 0.04)	.57	−0.02 (−0.07; 0.04)	.54	−0.02 (−0.07; 0.03)	.42	−0.05 (−0.10; 0.00)	.03
Model 2								
Coronary calcification	0.02 (−0.04; 0.08)	.49	0.03 (−0.03; 0.08)	.39	0.01 (−0.05; 0.07)	.74	−0.06 (−0.12;−0.01)	.03
Aortic arch calcification	−0.02 (−0.07; 0.04)	.60	0.00 (−0.06; 0.05)	.94	0.01 (−0.05; 0.06)	.78	−0.05 (−0.10; 0.01)	.08
Extracranial carotid calcification	0.02 (−0.04; 0.08)	.57	−0.01 (−0.06; 0.05)	.84	0.04 (−0.02; 0.09)	.24	−0.05 (−0.10; 0.01)	.10
Intracranial carotid calcification	0.00 (−0.05; 0.06)	.88	−0.02 (−0.07; 0.04)	.53	−0.02 (−0.07; 0.04)	.58	−0.06 (−0.11;−0.01)	.03

Abbreviations: CWI, color word interference; LDST, letter–digit substitution task; CI, confidence interval; SD, standard deviation.
NOTE. Model 1: Adjusted for age, sex, time interval, and level of education. Model 2: As model 1, additionally adjusted for obesity, hypertension, diabetes mellitus, hypercholesterolemia, low HDL-cholesterol levels, smoking status, and *APOE* ε4-carrier status.
*Inverted scores; lower scores indicate worse performance.

Table 6
Calcification in different vessel beds and cognitive decline per single test (WFT and 15-WLT)

	WFT		15-WLT DR		15-WLT IR	
	Difference in Z-score (95% CI)	*P*	Difference in Z-score (95% CI)	*P*	Difference in Z-score (95% CI)	*P*
Per SD increase in:						
Model 1						
Coronary calcification	−0.03 (−0.08; 0.03)	.31	−0.04 (−0.09; 0.02)	.24	−0.04 (−0.10; 0.02)	.20
Aortic arch calcification	−0.01 (−0.06; 0.04)	.68	−0.02 (−0.08; 0.04)	.48	−0.03 (−0.08; 0.03)	.38
Extracranial carotid calcification	0.00 (−0.05; 0.05)	.88	−0.07 (−0.13;−0.02)	.01	−0.01 (−0.06; 0.05)	.76
Intracranial carotid calcification	−0.06 (−0.11;−0.01)	.03	−0.04 (-0.09; 0.02)	.18	−0.02 (−0.08; 0.03)	.44
Model 2						
Coronary calcification	−0.03 (−0.08; 0.03)	.36	−0.03 (−0.09; 0.03)	.34	−0.04 (−0.10; 0.02)	.20
Aortic arch calcification	0.00 (−0.05; 0.06)	.93	−0.01 (−0.07; 0.05)	.85	−0.02 (−0.08; 0.04)	.48
Extracranial carotid calcification	0.02 (−0.04; 0.07)	.55	−0.08 (−0.14; −0.02)	.01	−0.02 (−0.08; 0.04)	.49
Intracranial carotid calcification	−0.04 (−0.10; 0.01)	.10	−0.02 (−0.08; 0.04)	.47	−0.02 (−0.08; 0.04)	.44

Abbreviations: WFT, Word Fluency Task; WLT DR, 15-word learning test delayed recall; WLT IR, 15-word verbal learning test immediate recall; CI, confidence interval; SD, standard deviation.

NOTE. Model 1: Adjusted for age, sex, time interval, and level of education. Model 2: As model 1, additionally adjusted for obesity, hypertension, diabetes mellitus, hypercholesterolemia, low HDL-cholesterol levels, smoking status, and *APOE* ε4-carrier status.

performed multiple statistical tests which might have inflated our type I error. However, an important consideration here is that most tests are actually not completely independent (e.g. the various cognitive domains are correlated and calcification in the different vessels is correlated). Therefore, conventional corrections for multiple testing would be overconservative [32]. Another consideration is that calcification is only a part of the atherosclerotic plaque. Using nonenhanced CT it is not possible to visualize the complete atherosclerotic plaque area and thus potentially interesting information on additional plaque characteristics, such as shape, stenosis or ulceration could not be measured. Nonetheless, strong evidence suggests that CT-based calcification volume provides an adequate reflection of the total underlying plaque burden [33]. For the assessment of calcification we used two types of multidetector CT-scanners (16 slice and 64 slice CT), which could have influenced the measurements. However, post-hoc analyses with adjustment for scanner type did not change the results. Next, due to selective participation of younger and healthier subjects, our results may be underestimating true associations. We also note that structural neuroimaging was not available in all participants to aid in the diagnostic process. This could have led to potential misclassification of vascular dementia as AD. Yet, we expect this misclassification to be minimal, given that we always used all clinical information [34]. Finally, we did not have neuropathological confirmation of dementia.

We found that atherosclerotic calcification in multiple vessel beds was related to a higher risk of dementia. Several explanations may underlie this association. First, our findings could be explained by an intermediary role for stroke. Atherosclerosis is a powerful risk factor for stroke [35], and in turn stroke-patients have an almost twofold increased risk of dementia [6,36]. However, censoring at time of stroke changed little in our associations of calcification with incident dementia. A similar absence of an effect of stroke has been shown for the relationship between carotid intima-media thickness and dementia [9,10]. Another point of consideration is that atherosclerosis in the carotid artery represents the strongest location of atherosclerosis related to stroke [37,38]. In contrast, we found associations with dementia for other vessel beds as well. This also points toward our findings being independent from stroke. Actually, this suggests that generalized atherosclerosis, which probably is a better reflection of one's vascular status rather than localized atherosclerosis, is associated with dementia.

A second explanation linking atherosclerosis to dementia is subclinical small vessel disease [6,39]. Autopsy studies provide strong evidence that most patients with Alzheimer's disease show small vessel disease in their brain [6]. This includes infarcts, microinfarcts, microbleeds, demyelinization, and axonal damage [6]. In vivo imaging studies have shown that MRI-markers of small vessel disease, e.g. white matter lesions and lacunar infarcts, are associated with the risk of dementia [6,40,41]. We have previously demonstrated that atherosclerotic calcification in all four vessel beds is strongly associated with these MRI-markers of subclinical vascular brain disease [18]. Together, this points toward a role for small vessel disease in the association of atherosclerosis with dementia.

Finally, chronic hypoperfusion may explain the association between atherosclerosis and dementia, especially Alzheimer's disease [6]. As a consequence of slowly progressing structural changes of cerebral vessels due to atherosclerosis, cerebral perfusion is impaired which could lead to subclinical vascular brain disease on the one hand, but may also cause loss of functionality of the blood-brain barrier. This in turn might allow increased parenchymal deposition of beta-amyloid protein and/or impaired amyloid clearance and thereby the formation of amyloid plaques, an important characteristic of Alzheimer's disease [5,6,42].

Research on dementia is very often challenging due to the possibility of competing risks [9]. In our study competing risk due to mortality might explain the lack of association between coronary artery calcification and dementia. The coronary arteries are the single most important location of atherosclerosis for risk of cardiac events, including cardiac death [13]. It is therefore conceivable that persons in our study with the largest load of coronary calcification died of competing risks and therefore did not remain at risk to develop dementia. Indeed, post-hoc analyses revealed that especially coronary artery calcification was associated with mortality.

By investigating cognitive decline in addition to the endpoint of dementia, we managed to circumvent competing risks to a certain extent. We found that atherosclerotic calcification in all locations, including the coronary arteries, was associated with cognitive decline. Moreover, when we repeated our analyses after excluding persons who converted to dementia during follow-up, we found that the results remained unchanged. This implies that our results were unlikely to be driven by preclinical dementia, but that atherosclerosis already plays an important role in the early stages of cognitive deterioration, presumably already years before the possible conversion to clinical dementia. Whereas our study had a follow-up period of 6 years, others found carotid atherosclerosis to be associated with cognitive decline over a 10-year period [43,44]. These findings indicate a potential window of opportunity for treatment of atherosclerosis which could possibly delay or even stop the cognitive decline and ultimately aid in the prevention of dementia.

When investigating the cognitive tests separately, in general, we found small effects of calcification on the performance on the tests. In agreement with others [45], we found strong associations between atherosclerosis and the LDST, which primarily assesses processing speed. Yet, it was surprising that we did not find strong associations between atherosclerosis and executive function [43,45]. This might be because our assessment of executive function was not detailed or sensitive enough to assess small changes. In our test battery there was namely only one test that primarily investigated executive function; the WFT. We only found an association of intracranial carotid artery calcification with this test.

In conclusion, our findings further establish the role of atherosclerosis in the etiology of dementia and cognitive decline. This calls for studies evaluating whether interventions targeted at reducing or stabilizing atherosclerosis would have a beneficial effect on the occurrence of dementia.

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Conflicts of interest/Disclosures: None.

Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jalz.2014.05.1758.

RESEARCH IN CONTEXT

1. Systematic review: We searched PubMed for relationships between atherosclerosis and dementia or cognition. We found multiple cross-sectional studies showing associations of atherosclerosis (restricted to one location) with cognition or dementia. Longitudinal data are nevertheless scarce, and it remains unclear whether atherosclerosis in different vessel beds differentially affects cognition and dementia.
2. Interpretation: We found that atherosclerosis, in particular in the extracranial carotid arteries, is related to a higher risk of dementia. We also found that atherosclerosis plays an important role in the process of cognitive deterioration, presumably already years before the possible conversion to dementia. This indicates a potential window of opportunity for treatment of atherosclerosis which could delay or possibly stop the cognitive decline and ultimately aid in preventing dementia.
3. Future directions: Important lines of future research should focus on the predictive value of atherosclerosis for dementia, and on the evaluation of treatment strategies for atherosclerosis with regard to the occurrence of dementia.

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Supplementary Table 1
Vascular risk profiles across participants in the current study samples and the total Rotterdam Study cohort

	Rotterdam Study-participants in present analyses		Other Rotterdam Study-participants*
Variable	N = 2364	N = 1847	N = 3686
Women	52.3%	52.9%	63.1%
Age, yrs	69.4 (6.7)	68.4 (5.9)	75.3 (7.6)
Obesity	23.9%	23.8%	18.3%
BMI, kg/m^2	27.7 (3.9)	27.7 (3.9)	27.5 (4.3)
Hypertension	73.7%	72.3%	79.0%
Systolic blood pressure, mmHg	146.7 (20.1)	145.6 (19.1)	152.1 (22.1)
Diastolic blood pressure, mmHg	80.3 (10.7)	80.1 (10.4)	79.3 (11.2)
Diabetes	11.2%	10.1%	14.9%
Serum glucose, mmol/L	5.7 (1.3)	5.7 (1.2)	6.0 (1.6)
Hypercholesterolemia	48.6%	49.1%	40.0%
Serum total cholesterol, mmol/L	5.7 (1.0)	5.7 (1.0)	5.6 (1.0)
Low HDL cholesterol	10.6%	10.0%	7.4%
Serum HDL cholesterol, mmol/L	1.4 (0.4)	1.4 (0.4)	1.5 (0.4)
Smoking, ever	67.5%	66.9%	65.2%
APOE ε4-carriers	25.6%	25.1%	25.6%

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; *APOE*, apolipoprotein E.

NOTE. Values are means (standard deviations) for continuous variables and percentages for dichotomous variables.

*These are all other Rotterdam Study-participants that participated in the follow-up visit [n = 6050 (all), 2364 (current study) = 3686].

Supplementary Table 2
Calcification in different vessel beds and cognitive decline after excluding persons who suffered a stroke (upper panel) or developed dementia (lower panel)

	Global cognition		MMSE	
	Difference in Z-score (95% CI)	*P*	Difference in points (95% CI)	*P*
Per SD increase in:				
Stroke excluded (n = 90)				
Coronary calcification	−0.03 (−0.05; 0.00)	.06	−0.11 (−0.21;−0.01)	.03
Aortic arch calcification	−0.02 (−0.05; 0.00)	.10	−0.07 (−0.17; 0.03)	.15
Extracranial carotid calcification	−0.02 (−0.05; 0.01)	.13	−0.02 (−0.12; 0.08)	.69
Intracranial carotid calcification	−0.04 (−0.07; −0.02)	<.01	−0.07 (−0.16; 0.03)	.19
Dementia excluded (n = 42)				
Coronary calcification	−0.03 (−0.06; −0.01)	.02	−0.13 (−0.22; −0.03)	<.01
Aortic arch calcification	−0.02 (−0.05; 0.00)	.09	−0.09 (−0.18; 0.00)	.06
Extracranial carotid calcification	−0.03 (−0.05; 0.00)	.05	−0.03 (−0.12; 0.06)	.47
Intracranial carotid calcification	−0.04 (−0.06; −0.01)	<.01	−0.09 (−0.18; 0.00)	.05

Abbreviations: CI, confidence interval; SD, standard deviation; n, number of cases.

NOTE. Adjusted for age, sex, time interval and level of education.