Intracranial Vessel Wall Lesions on 7T MRI (Magnetic Resonance Imaging)

Occurrence and Vascular Risk Factors: The SMART-MR Study

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Background and Purpose—Intracranial vessel wall lesions are a novel imaging marker of intracranial atherosclerosis (ICAS), but data on their occurrence and risk factors are lacking. Our aim was to study the frequency, distribution, and risk factors of intracranial vessel wall lesions on 7T magnetic resonance imaging in patients with a history of vascular disease.

Methods—Within the SMART-MR study (Second Manifestations of Arterial Disease-Magnetic Resonance), cross-sectional analyses were performed in 130 patients (68±9 years) with assessable 7T intracranial vessel wall–magnetic resonance imaging data. Associations between vascular risk factors and ICAS burden, defined as the total number of vessel wall lesions, were estimated using linear regression analyses with ICAS burden as the dependent variable, adjusted for age and sex.

Results—Ninety-six percent of patients had ≥1 vessel wall lesion. The mean±SD (range) ICAS burden was 8.5±5.7 (0–32) lesions. Significant associations were found between ICAS burden and age (*b*=2.0 per +10 years; 95% CI, 0.81– 3.10), systolic blood pressure (*b*=0.9 per +10 mm Hg; 95% CI, 0.27–1.42), diabetes mellitus (*b*=3.2 for presence of diabetes mellitus; 95% CI, 0.79–5.72), hemoglobin A1c level (*b*=1.2 per +1%; 95% CI, 0.19–2.26), apoB (apolipoprotein-B) (*b*=4.7 per +1 g/L; 95% CI, 0.07–9.35), and hs-CRP (high-sensitivity C-reactive protein) level (*b*=2.7 for hs-CRP >3 mg/L; 95% CI, 0.22–5.11). No significant associations were found with sex, smoking, and other lipid-factors.

Conclusions—Vessel wall lesions are a novel and direct magnetic resonance imaging marker of ICAS. In this cohort, 96% of patients had at least 1 lesion on 7T vessel wall–magnetic resonance imaging. More lesions were found with older age, higher systolic blood pressure, diabetes mellitus, and higher levels of hemoglobin A1c, apoB, and hs-CRP. **(*Stroke*. 2019;50:88-94. DOI: 10.1161/STROKEAHA.118.022509.)**

Key Words: blood pressure ■ diabetes mellitus ■ intracranial atherosclerosis ■ magnetic resonance imaging ■ risk factors

Intracranial atherosclerosis (ICAS) is characterized by the development and progression of atherosclerotic plaques in the intracranial arteries. Symptomatic ICAS is one of the leading causes of ischemic stroke worldwide and as such responsible for considerable morbidity and mortality.[1,2] Other complications are an increased risk of recurrent stroke, transient ischemic attacks, and dementia.[1,3] Studies report widely varying prevalence estimates of ICAS, ranging from 3% to 95%, depending on the specific population studied and imaging methods used.[4]

Intracranial arterial vessel wall lesions are a novel and direct marker of ICAS that can be imaged using high-resolution vessel wall–magnetic resonance imaging (MRI). Vessel wall lesions have several potential advantages over conventional indirect markers, such as stenosis and calcification.[5] First, both stenotic and nonstenotic ICAS can be visualized, enabling a more complete assessment of ICAS burden.[6] Furthermore, cerebral arteries do not calcify distal to the circle of Willis arteries, limiting assessment of this marker to the proximal arteries. Also, the exact cause of calcification remains uncertain and may in part be unrelated to atherosclerosis.

Vessel wall–MRI studies have mainly been aimed at technical advancements, plaque characterization, and diagnostic efficacy.[7,8] To date, only one study has reported on the risk factors and prevalence of vessel wall lesions.[9] Assuming these to be identical to those of conventional ICAS markers may limit its utility. Also, risk factors and prevalence estimates differ between vessel wall lesions, calcification, and stenosis.[5,9,10] Age, diabetes mellitus, hypertension, and systolic blood pressure seem to show consistent associations with different ICAS

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A list of all SMART Study Group members is given in the Appendix.

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markers. However, a definite risk factor model remains to be established.[11]

This study had 2 main objectives. First, to study the frequency, distribution, and burden of intracranial vessel wall lesions, assessed by means of intracranial vessel wall–MRI at 7T, in a population of patients with a history of vascular disease and second, to explore possible risk factors of this novel and direct marker of ICAS and relate these to known ICAS risk factors.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

Data were used from the SMART-MR study (Second Manifestations of Arterial Disease-Magnetic Resonance), which is a prospective cohort study at our institution with the aim to investigate risk factors and clinical correlates of MRI neuroimaging markers in patients with vascular disease.[12] In brief, from 2001 to 2005, 1309 patients newly referred to our institution with coronary artery disease, cerebrovascular disease, peripheral artery disease, or abdominal aortic aneurysm, and without MRI contraindications were enrolled in the SMART-MR study. On a 1-day visit to our institution's hospital, the participants received a 1.5T MRI of the brain, a physical examination, ankle-brachial index assessment, ultrasonography of the carotid arteries, blood and urine sampling, and questionnaires to assess risk factors, medical history, and daily functioning.[13] All risk factors were assessed on the same day. Follow-up exams of the SMART-MR cohort were performed from 2006 to 2009 (first follow-up), and 2013 to 2017 (second follow-up).

A flowchart of the study sample is presented in Figure I in the online-only Data Supplement. In brief, from June 2016 to October 2017, during the second follow-up period, a vessel wall–MRI sequence was performed, as part of a standard 7T MRI of the brain. All patients who had received vessel wall imaging during this timeframe were included. A total of 147 patients were included, of which 17 were excluded because of artifacts inhibiting vessel wall assessment of ≥1 major segment of the circle of Willis (major segments included the distal internal carotid artery and primary branches [M1, A1, P1] of the anterior, middle, and posterior cerebral artery), leaving 130 patients for final analysis. Note, 7T MRI was performed on average 13±1 years after baseline measurements. Risk factor assessment, including questionnaire data and blood and urine sampling, was performed median 2.3 (range, 0.6–8.6) years before the 7T MRI.

Comparison of age and sex between excluded and included patients showed that excluded patients were older, although this did not reach statistical significance (70±7 versus 68±9 years; P=0.11). Sex distribution did not differ (88% versus 88% male; P=0.95).

The SMART-MR study was approved by the institutional review board of our institution, and written informed consent was obtained from all participants.

Vascular Risk Factors

See the online-only Data Supplement.

MR Imaging

For MRI, a 7T whole-body system (Philips Healthcare, Cleveland, OH) was used with a volume/transmit coil for transmission and a 32-channel receive head coil (Nova Medical, Wilmington, MA). Intracranial vessel wall imaging was performed with a T_1-weighted Magnetization-Prepared Inversion Recovery Turbo Spin Echo sequence, with the following parameters: field-of-view 250×250×190 mm^3, acquired resolution 0.8×0.8×0.8 mm^3 (reconstructed to 0.49×0.49×0.4 mm^3), repetition time/inversion time/echo time 3952/1375/37 ms, acquisition time 10:40 minutes. A more detailed description of this MR sequence can be found elsewhere.[14] A maximum intensity projection of the first echo of a dual echo susceptibility-weighted imaging sequence was used as a faux MR angiography, with the following parameters: repetition time/echo time 1/echo time 2, 20/6.9/15.8 ms; field-of-view 200×200×120 mm^3; acquired resolution 0.5×0.5×0.7 mm^3 (reconstructed to 0.4×0.4×0.35 mm^3); flip angle 12°; acquisition time, 09:17 minutes.

Assessment of ICAS

For image assessment, transverse multiplanar reconstructions were made from the T_1-weighted Magnetization-Prepared Inversion Recovery Turbo Spin Echo sequence (slice thickness 0.8 mm; no slice gap), all angulated according to the nasion-foramen magnum line, and using a standalone workstation (Philips Healthcare, Cleveland, OH).

All images were assessed, blinded to patient characteristics, by 1 observer (Dr Zwartbol) who was trained by a senior observer with 8 years of experience in reading intracranial vessel wall images (Dr van der Kolk). Training was based on a practice set of 15 patients from the IVI study (Intracranial Vessel Wall Imaging), a study population of patients with anterior circulation ischemic stroke and transient ischemic attack[15] and a consensus set of 20 patients from the current study. An interobserver agreement was calculated between Drs van der Kolk and Zwartbol using the dice similarity coefficient based on results from the consensus set. A coefficient of 0.75 was achieved and was regarded as good.

Vessel wall lesions were rated according to criteria described previously.[16] In short, a vessel wall lesion was defined as either a clear focal or more diffuse thickening of the vessel wall, compared with the healthy contralateral or neighboring vessel wall. Inconspicuous lesions were evaluated in multiple planes for verification. Vessel wall lesions were rated per arterial segment, which included: the anterior cerebral arteries (A1, A2 segments), middle cerebral arteries (M1, M2 segments), distal internal carotid arteries (ICA; supraclinoid (C6) and communicating segment (C7), posterior communicating arteries, posterior cerebral arteries (P1, P2 segments, P1-P2 bifurcation), basilar artery, and vertebral arteries. Arterial segments could contain multiple lesions. Lesions in bifurcations that stretched into multiple segments (eg, from C7 segment into M1 segment) were counted as separate lesions for each affected segment. The maximum intensity projection of the susceptibility-weighted imaging was used as a faux MR angiography to assess the course of the smaller arterial segments (M2, A1, P2, posterior communicating arteries). However, because of its sensitivity to artifacts (flow-related signal loss, susceptibility effects), we could not use it to reliably measure luminal stenosis.

Statistical Analysis

First, characteristics of the study sample were calculated. Second, frequencies and distribution characteristics of vessel wall lesions were calculated per arterial segment, artery, and circulatory region. Third, linear regression analysis was used to estimate associations between vascular risk factors and ICAS burden. Adjustments were made for age and sex. A sensitivity analysis was performed to control for the time interval (in days) between the date of risk factor measurements and date of the 7T MRI. Residual plots of all analyses were checked for regression assumptions. Alcohol use was entered into the model as a categorical variable (<1, 1–10, or ≥11 units per week). Smoking was entered into the model as a continuous (pack-years) or categorical (never, former, or current) variable. Body mass index was entered as a continuous variable and also dichotomized by clinical cutoff for obesity (cutoff ≥30 kg/m^2). Hs-CRP (high-sensitivity C-reactive protein) was entered as a continuous variable and as a dichotomous variable (cutoff >3 mg/L).[17] *APOE*-ε4 allele status was entered into the model as a dichotomous variable: ≥1 ε4 allele versus no presence. Statistical analyses were performed using IBM SPSS Statistics version 21 for Windows (IBM Corporation, Armonk, NY).

Results

Characteristics of the 130 patients in our study sample (68±9 years; 88% male) are presented in Table 1. Ninety-six percent of patients had evidence of ≥1 vessel wall lesion. A mean number of 8.5±5.7 vessel wall lesions (median 7; range 0–32) were identified in the total cerebral circulation, with 5.3±3.2 lesions (median 4; range 0–14) in the anterior and 3.8±3.0 (median 3; range 0–18) in the posterior circulation (Table 2). A higher ICAS burden was found in patients with a history of cerebrovascular disease (10.9±7.4 versus 7.3±4.9 lesions; P=0.01). On the arterial level, lesions were most frequently identified in the distal ICAs (70% [left]–62% [right] of patients) and basilar artery (59%). Figure 1 provides a schematic overview of the distribution and frequency of vessel wall lesions per segment. Examples of intracranial vessel wall lesions on MRI are provided in Figure 2. A more detailed overview of the number of vessel wall lesions per segment, artery, and circulatory region is provided in Table I in the online-only Data Supplement.

Table 3 reports the association between conventional vascular risk factors and ICAS burden. Increasing age was associated with a higher ICAS burden (b=2.0 lesions per +10 years; 95% CI, 0.81–3.10). Also, a significant association was observed between increasing systolic blood pressure and ICAS burden (b=0.9 lesions per +10 mm Hg; 95% CI, 0.27–1.42). No significant association was found between sex, smoking, alcohol intake, diastolic blood pressure or hypertension, and ICAS burden.

Table 4 reports the association between metabolic and miscellaneous vascular risk factors with ICAS burden. Several metabolic risk factors were found to be significantly associated with a higher ICAS burden, namely diabetes mellitus (b=3.2 for presence of diabetes mellitus; 95% CI, 0.79–5.72), hemoglobin A1c level (b=1.2 lesions per +1%; 95% CI, 0.19–2.26), and apoB (apolipoprotein-B) (b=4.7 per +1 g/L; 95% CI, 0.07–9.35). Although positive trends were seen for obesity, metabolic syndrome, hyperlipidemia, total cholesterol levels, and triglyceride levels, these did not reach statistical significance. In regards to miscellaneous risk factors, a significant association was found between increased hs-CRP and ICAS burden (b=2.7 for hs-CRP >3.0 mg/L; 95% CI, 0.22–5.11), when compared with normal hs-CRP (≤3.0 mg/L). No association was found between presence of ≥1 *APOE*-ε4 allele and ICAS burden.

As a sensitivity analysis, all models were additionally adjusted for the time interval between risk factors measurement and date of 7T MRI. Tables II and III in the online-only Data Supplement present the results of these analyses. As can be seen, although the estimates somewhat differed, this did not lead to different conclusions.

Eccentric Versus Concentric Vessel Wall Lesions

An extensive overview of the number and ratio of eccentric and concentric vessel wall lesions is provided in Table IV in the online-only Data Supplement. Eccentric lesions were

Table 1. Vascular Risk Factors in Study Population (N=130)

Conventional vascular risk factors	
Age, y	68±9
Male sex	88%
Smoking status	
Current smoker	15%
Former smoker	71%
Pack-years	21.7±18.4
Alcohol intake, units/wk	2.0±1.0
Hypertension	90%
Systolic blood pressure, mm Hg	139±17
Diastolic blood pressure, mm Hg	79±9
Metabolic vascular risk factors	
BMI (kg/m^2)	27.3±3.7
Obesity*	21%
Hyperlipidemia	93%
Triglycerides, mmol/L	1.5±0.7
LDL-C, mmol/L	2.4±0.8
HDL-C, mmol/L	1.3±0.4
Total cholesterol, mmol/L	4.4±0.9
ApoB, g/L	0.8±0.2
Diabetes mellitus	19%
HbA1c, %	5.9±0.9
Fasting glucose, mmol/L	6.3±1.7
Metabolic syndrome	52%
Miscellaneous vascular risk factors	
hs-CRP, mg/L	2.6±3.7
hs-CRP >3 mg/L	20%
≥1 *APOE*-ε4 allele	31%
History of vascular disease†	
Cerebrovascular disease	25%
Coronary artery disease	79%
Abdominal aortic aneurysm	2%
Peripheral artery disease	19%

Values are presented as mean±SD for continuous variables and frequencies (%) for dichotomous variables. ApoB indicates apolipoprotein-B; BMI, body mass index; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; and LDL-C, low-density lipoprotein cholesterol.

*BMI ≥30 kg/m^2.

†Twenty-five percent of 130 patients had >1 vascular disease. Seven percent had cerebrovascular disease only.

Table 2. Overview of Frequency and Statistical Dispersion of Arterial Wall Lesions in Circulatory Regions in Study Population

Circulatory Region	Frequency	Median (range)	Mean±SD
Total circulation	96%	7 (0–32)	8.5±5.7
Anterior circulation	92%	4 (0–14)	5.3±3.2
Posterior circulation	88%	3 (0–18)	3.8±3.0

A complete overview, including data of individual arteries and segments, is provided in Table I in the online-only Data Supplement.

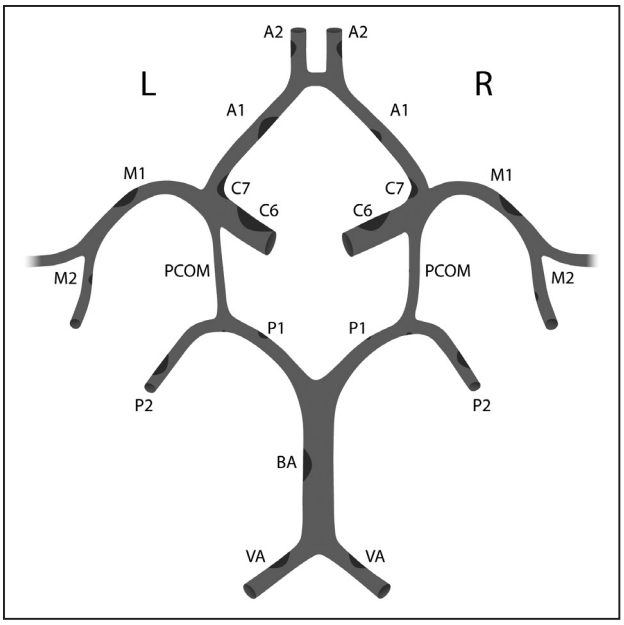

Figure 1. Schematic drawing of the circle of Willis and its branches, with the frequency of intracranial vessel wall lesions in the current study population illustrated by means of plaques: a larger plaque indicates a higher frequency of lesions within the specific segment (Table I in the online-only Data Supplement). **Left** (L): C6=63.1%; C7=42.3%; A1=35.4%; A2=30.0%; M1=49.2%; M2=20.0%; vertebral artery (VA)=38.5%; P1=19.2%; P1-P2 bifurcation=6.2%; P2=37.7%; posterior communicating artery (PCom)=2.3%. **Middle**: basilar artery (BA)=58.5%. **Right** (R): C6=56.2%; C7=38.5%; A1=21.5%; A2=30.8%; M1=43.1%; M2=16.9%; VA=30.0%; P1=9.2%; P1-P2 bifurcation=12.3%; P2=31.5%; PCom=5.4%.

found in 95% of patients, whereas concentric lesions were found in 26% of patients. Furthermore, 75% of all lesions were eccentric compared with 25% for concentric lesions. The age- and sex-adjusted relative risk of concentric lesions increased significantly with increasing numbers of eccentric lesions (relative risk, 1.03 per +1 eccentric lesion; 95% CI, 1.01–1.04).

Discussion

In this cohort of 130 patients with a history of vascular disease, >95% of patients had at least 1 intracranial vessel wall lesion. Risk factors for these vessel wall lesions were older age, higher systolic blood pressure, diabetes mellitus, and increased hemoglobin A1c, apoB, and hs-CRP levels. A trend was found for obesity, hyperlipidemia, metabolic syndrome, and higher total cholesterol and triglyceride levels.

Recently, the ARIC study (Atherosclerosis Risk in Communities) was the first study to use high-resolution vessel wall–MRI at 3T to assess vessel wall lesions, as a measure of ICAS, in a large population-based cohort and reported a prevalence of ≥1 vessel wall lesion in 36% of participants.[9] This was higher than prevalence estimates from prior population-based studies based on detection of (hemodynamic) stenosis, which reported estimates from 3% to 15%.[1] In cohorts with vascular risk this increases to 13% to 21% and tops out at 40% to 67% in ischemic stroke patients.[1] Studies based on intracranial calcifications report estimates up to 80%, although the exact cause of this marker is uncertain.[5] Our reported high frequency of 96% is likely because of 2 factors. First, our cohort consisted of vascular disease patients, and 88% were male. Hence, assuming ICAS has similar determinants as extracranial atherosclerosis, they are likely at risk of developing ICAS. Second, although our reconstructed spatial resolution is similar to the ARIC study, the increased MR signal at 7T was used to optimize the contrast-to-noise ratio, which may have enabled us to grade lesions with more certainty. All current vessel wall sequences are limited because of partial volume averaging. Increased contrast-to-noise ratio counteracts this limitation and likely reduces both false-positives and false-negatives.[18] Of note, 75% of our population had symptomatic atherosclerosis in extracranial arteries only. Although the mean ICAS burden in this group was lower than in patients with cerebrovascular disease, it was still considerable and underlines that atherosclerosis is a generalized disease with varying symptomatic arteries.

A relatively regular distribution of vessel wall lesions was found, with the highest frequency in both distal ICAs and the basilar artery, which is in concordance with previous studies.[15,19,20] Most lesions were of the eccentric type, although in the anterior cerebral arteries and vertebral arteries, concentric lesions occurred with a similar frequency. Furthermore, increasing numbers of eccentric lesions were associated with a higher risk of concentric lesions. This finding seems to suggest that concentricity is related to the overall severity of ICAS. Several factors may explain the higher frequency of lesions in the ICAs and basilar artery. First, it is thought that the proximal intracranial arteries—as opposed to the remaining intracranial vasculature—still

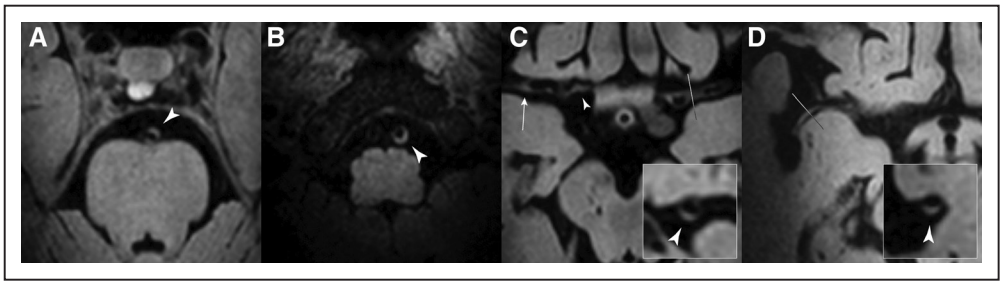

Figure 2. A 79-y-old male patient included with a history of coronary heart disease. On T1-weighted Magnetization-Prepared Inversion Recovery Turbo Spin Echo vessel wall–magnetic resonance imaging multiple lesions are identified (**A**–**D**). **A**, Vessel wall lesion of the basilar artery (arrowhead). **B**, Vessel wall lesion of the distal left vertebral artery (arrowhead) with normal right vertebral artery. **C**, Bilateral M1 vessel wall lesions (arrow, and arrowhead in sagittal multiplanar reconstruction in enclosed panel). Also, note lesion in the proximal right A1 segment (small arrowhead). **D**, Vessel wall lesion in the proximal right M2 segment.

Table 3. Association of Conventional Risk Factors With ICAS Burden

	ICAS Burden, *b* (95% CI)	*P* Value
Male sex	1.31 (–1.65–4.26)	0.384
Age, per +10 y	1.96 (0.81–3.10)	0.001
Smoking status		
Never smoker	0 (reference)	
Former smoker	0.21 (–2.68–3.09)	0.887
Current smoker	0.24 (–3.40–3.89)	0.895
Pack-years, per +10 y	0.33 (–0.20–0.86)	0.224
Alcohol intake		
No or 1< unit/wk	0 (reference)	
1–10 units/wk	–0.87 (–3.33–1.59)	0.486
≥11 units/wk	–1.36 (–4.08–1.37)	0.326
Hypertension, y/n	–0.83 (–4.12–2.47)	0.620
Blood pressure, per +10 mm Hg		
Systolic	0.85 (0.27–1.42)	0.004
Diastolic	0.51 (–0.59–1.61)	0.361

b values are unstandardized linear regression coefficients adjusted for age and sex. ICAS indicates intracranial atherosclerosis; and y/n, yes versus no.

possess vasa vasorum, which facilitates arterial wall functioning and plays a critical role in atherogenesis via initiation of an inflammatory cascade. Second, the distal ICA is a segment exposed to low shear stress, which is a hemodynamic risk factor for plaque formation.[21] Third, the distal ICA and the basilar artery have the largest radius of all intracranial arteries, which has been associated with the degree of atherosclerosis.[19] Of course, lesions are harder to detect in smaller arteries. However, when grading lesions, the distal, proximal, and contralateral healthy segment was used as reference, as a way to mitigate this limitation which is inherent to current spatial resolutions. Lastly, it should be noted that artifacts hindered assessment of the vertebral arteries in 20% to 24% of cases and M2 segments in 6% to 9% of cases (Table I in the online-only Data Supplement). Therefore, the prevalence of vessel wall lesions at these locations may be higher than reported.

Table 4. Association of Metabolic and Miscellaneous Risk Factors With ICAS Burden

	ICAS Burden, *b* (95% CI)	*P* Value
BMI, per +1 kg/m^2	0.10 (–0.18–0.38)	0.463
Obesity*, y/n	2.31 (–0.22–4.83)	0.073
Hyperlipidemia, y/n	3.37 (–0.49–7.22)	0.087
Triglycerides, per +1 mmol/L	1.28 (–0.16–2.72)	0.082
LDL-C, per +1 mmol/L	1.00 (–0.23–2.23)	0.110
HDL-C, per +1 mmol/L	–0.23 (–3.04–2.58)	0.815
Total cholesterol, per 1 mmol/L	1.03 (–0.03–2.10)	0.057
ApoB, per +1 g/L	4.70 (0.07–9.35)	0.047
Diabetes mellitus, y/n	3.24 (0.79–5.72)	0.010
HbA1c, per % increase	1.22 (0.19–2.26)	0.021
Glucose, per +1 mmol/L	0.39 (–0.18–0.97)	0.180
Metabolic syndrome, y/n	1.85 (–0.10–3.80)	0.062
≥1 *APOE*-ε4 allele, y/n	–1.48 (–3.63–0.67)	0.175
hs-CRP, per +1 mg/L	0.02 (–0.26–0.30)	0.882
hs-CRP >3 mg/L, y/n	2.67 (0.22–5.11)	0.033

b values are unstandardized linear regression coefficients adjusted for age and sex. ApoB indicates apolipoprotein-B; BMI, body mass index; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; ICAS, intracranial atherosclerosis; LDL-C, low-density lipoprotein cholesterol; and y/n, yes versus no.

*BMI ≥ 30 kg/m^2.

Older age, higher systolic blood pressure, diabetes mellitus, higher hemoglobin A1c and apoB levels, and hs-CRP >3 mg/L were associated with more vessel wall lesions, which is largely in concordance with previous studies based on arterial stenosis detection.[4,22,23] In the ARIC study, which tested associations between midlife risk factors and late-life ICAS (stratified by race), presence of vessel wall lesions was associated with age, midlife hypertension, and hyperlipidemia in both blacks and whites. Sex, midlife smoking, and diabetes mellitus were exclusively associated with vessel wall lesions in blacks. Analysis with late-life risk factors, which more closely resembles our analysis, failed to show an association, which they note could partly stem from reverse causation.[9] Our results are partly in concordance with their findings, although we did not find a significant association with hyperlipidemia. However, hyperlipidemia, obesity, metabolic syndrome, higher total cholesterol, and triglyceride levels all showed a statistical trend with more vessel wall lesions. No significant relationship was found with sex, hypertension, cigarette smoking, alcohol intake, other cholesterol levels (HDL-C [high-density lipoprotein cholesterol], LDL-C [low-density lipoprotein cholesterol]), and *APOE*-ε4 allele status. Several factors may explain the absent or marginal associations between vessel wall lesions and these risk factors. First, the relationship of these factors with conventional markers, such as arterial stenosis and calcification, is also uncertain,[4,9–11,24–33] and most were also not found in the ARIC study. In regard to lipid-related determinants, a reduced susceptibility of the intracranial arteries to cholesterol-induced atherogenesis might explain these inconsistencies.[34] Second, because of the follow-up design of the SMART study, changes in lifestyle, and start of medical treatment because of risk factors detected at baseline is likely to weaken associations with those risk factors. Third, the modest size of our cohort, although large for a clinical 7T study, may have reduced statistical power to find significant associations, especially for dichotomous variables with highly skewed frequency distributions, such as sex and hypertension. Fourth, our use of a cumulative burden score might favor certain risk factors and attenuate the relationship with others. For example, intima-media thickening is a more diffuse multifocal process and is linearly related to systolic blood pressure.[35] Stenosis is a more focal advanced lesion and closely associated with lipid disorders.[36] Following from this, our score would favor risk factors which are related to more lesions and not so much the severity of a focal lesion. Lastly, because of a lack of radio-pathological correlation

studies, it is uncertain if all lesions observed in our study are of atherosclerotic cause.

To date, the ARIC study is the only other study that has investigated intracranial vessel wall lesions in nonstroke patients in vivo using vessel wall–MRI. Although the associations between vessel wall lesions and common cardiovascular risk factors in both the ARIC and our study are similar, the novelty of our results lies in the fact that almost all included subjects showed vessel wall lesions, compared with 36% of patients in the ARIC study. Although this result indeed confirms previous reports of pathological studies, this confirmation also suggests that 7T vessel wall–MRI can visualize the real lesion burden because of its high spatial resolution and contrast-to-noise ratio. One could argue that the additional, possibly smaller lesions that we see at 7T may not always be clinically relevant and perhaps represent normal aging; however, the observation that correlations with risk factors remained even for this high percentage of subjects with vessel wall lesions suggests that the majority of these lesions are representative of the total vessel wall lesion burden. The impact of this study lies in that 7T vessel wall–MRI seems to be able to visualize the total intracranial vessel wall lesion burden, compared with 3T MRI which only shows vessel wall lesions in a relatively small percentage of patients. This may also suggest that 7T MRI, not 3T MRI, should be used, for example, screening of vessel wall lesions in patient populations with increased risks. Nonetheless, the clinical implications of these lesions are not yet clear, and long-term prospective studies are needed to investigate whether the observed total lesion burden will be clinically relevant, or whether other factors like enhancement and other lesion characteristics play a more prominent role.

Future studies on ultra-high field vessel wall imaging could focus on updating current MRI sequences, to keep up with advancements at lower field strengths and more extensive histopathologic validation studies. In addition, more complex multiparametric scores, such as the Gensini-score for coronary heart disease, are an interesting direction of research which should be further explored. Current multisequence neurovascular MRI protocols can assess the number, location, stenosis, and biology of ICAS lesions. Hence, with the prevalence and functional impact of ICAS becoming more apparent, and the advent of therapeutic options, multiparametric scores like these will provide a more versatile way to study the relationship between treatment of risk factors, ICAS, and outcomes. Furthermore, because ICAS phenotypes differ between ethnic populations, studies could investigate if tailoring multisequence MRI protocols to the patients' ethnicity improves effectiveness and efficiency of the study. Finally, and this is relevant both for 3T and 7T intracranial vessel wall imaging, there will be a need for longitudinal studies investigating the clinical relevance of the visualized vessel wall lesions.

Our study has several strengths. First, the increased MR signal at 7T field strength was used to optimize the contrast-to-noise ratio and enabled accurate visualization of wall pathology. Second, the large coverage area allowed assessment of the circle of Willis branches over a great length. Hence, with regard to the assessment of ICAS in general, one could argue that it enabled a more complete assessment compared with studies based on calcification, which is limited to the large cerebral arteries and stenosis, which ignores nonstenotic pathology. Furthermore, completeness of data on a variety of determinants allowed us to perform extensive exploratory analysis. Lastly, our ICAS burden metric is a basic uniparametric score, which makes it robust and easy to understand and implement. However, it is also limited, because it lacks information on luminal stenosis, which cannot accurately be measured. Also, we did not use any other sequences specifically aimed at characterization of the vessel wall; including this information might have additional value in the development of future multiparametric scores. Apart from the already mentioned limitations, the cross-sectional design is also a limitation because it prohibits conclusions on causality. Furthermore, because of logistic reasons, the risk factor assessment and the 7T MRI were not performed on the same day and in many participants the time interval was large. As risk factor status could have changed during this interval, this may have influenced the observed associations. However, when we adjusted for this interval, we did not find relevant differences in association estimates and CIs. Lastly, we included participants who were part of a longitudinal study and who were willing and able to undergo a 7T MRI on average 13±1 years after baseline. Most likely, the study sample consisted of the relatively healthy participants of the original SMART-MR cohort.

In conclusion, intracranial vessel wall lesions are a novel MRI marker of ICAS that offers a more direct approximation of disease burden than conventional indirect markers, such as arterial stenosis and calcification. We have shown, using 7T vessel wall–MRI, that these focal thickenings of the intracranial arterial walls are a highly common occurrence in middle-aged and older men and women with a history of vascular disease and that they have similar but not identical risk factors compared with conventional ICAS markers.

Appendix

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Disclosures

None.

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