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Cardiovascular risk scoring and magnetic resonance imaging detected subclinical cerebrovascular disease

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Cardiovascular risk factors are used for risk stratification in primary prevention. We sought to determine if simple cardiac risk scores are associated with magnetic resonance imaging (MRI)-detected subclinical cerebrovascular disease including carotid wall volume (CWW), carotid intraplaque haemorrhage (IPH), and silent brain infarction (SBI).

**Methods and results**

A total of 7594 adults with no history of cardiovascular disease (CVD) underwent risk factor assessment and a non-contrast enhanced MRI of the carotid arteries and brain using a standardized protocol in a population-based cohort recruited between 2014 and 2018. The non-lab-based INTERHEART risk score (IHRS) was calculated in all participants; the Framingham Risk Score was calculated in a subset who provided blood samples \( n = 3889 \). The association between these risk scores and MRI measures of CWW, carotid IPH, and SBI was determined. The mean age of the cohort was 58 (8.9) years, 55% were women. Each 5-point increase \((\sim 1 \text{ SD})\) in the IHRS was associated with a 9 mm\(^3\) increase in CWW, adjusted for sex \( (P < 0.0001) \), a 23% increase in IPH \( (95\% \text{ confidence interval} \ (9.0\% - 38\%)) \), and a 32% \( (95\% \text{ CI} \ 20\% - 45\% ) \) increase in SBI. These associations were consistent for lacunar and non-lacunar brain infarction. The Framingham Risk Score was also significantly associated with CWW, IPH, and SBI. CWW was additive and independent to the risk scores in its association with IPH and SBI.

**Conclusion**

Simple cardiovascular risk scores are significantly associated with the presence of MRI-detected subclinical cerebrovascular disease, including CWW, IPH, and SBI in an adult population without known clinical CVD.

**Keywords**

magnetic resonance imaging • atherosclerosis • silent brain infarction • risk factors
are primarily related to small vessel disease, versus larger (>15 mm axial diameter) or cortical infarcts, which may be caused by embolism.25

Carotid arteries

Carotid artery vessel wall volume (mm³) (left, right, and combined) within a 32-mm vessel length centred on each carotid bifurcation (to include distal common and proximal internal carotid arteries) was measured by subtracting lumen volume from total vessel volume. Carotid vessel wall volume was defined as the maximum of the left and right carotid vessel wall volumes and was used as a measure of atherosclerosis.13 IPH was determined by the presence of increased signal intensity within the carotid artery wall at least one voxel in size with a signal intensity at least a one and a half times higher than the adjacent sternocleidomastoid muscle. Calcification or necrotic lipid cores were not assessed in the MRI protocol.

Table 1  Demographic characteristics

|                         | Overall | Women | Men |
|-------------------------|---------|-------|-----|
| Number                  | 7594    | 4195  | 3399|
| Age (years)             | 57.8 (8.9) | 57.3 (8.7) | 58.4 (9.1) |
| Non-White (%)           | 19.6    | 19.6  | 19.7|
| Urban region (%)        | 97.5    | 97.3  | 97.8|
| Family history of MI (%)| 33.1    | 34.8  | 31.0|
| Elevated cholesterol (%)| 36.7    | 29.8  | 45.2|
| Self-reported history of diabetes (%) | 4.9 | 3.5 | 6.6 |
| Hypertension (%)        | 38.4    | 29.9  | 48.8|
| Blood pressure (mmHg)   |         |       |     |
| Systolic                | 129 (17)| 125 (17)| 134 (15) |
| Diastolic               | 79 (10) | 78 (10)| 82 (10)|
| Smoking status          |         |       |     |
| Current smoker (in past year) (%) | 5.4 | 5.2 | 5.6 |
| Former smoker (quit >1 year ago) (%) | 34.0 | 33.3 | 35.0 |
| Never smoked (%)        | 60.6    | 61.5  | 59.4|
| Second hand smoke exposure (1+ h/week) (%) | 4.6 | 4.7 | 4.4 |
| Abdominal obesity (WHR) %| 50.5    | 37.7  | 66.4|
| Leisure physical inactivity (%) | 39.5 | 43.4 | 34.7|
| Poor diet quality (%)   | 16.8    | 13.2  | 21.2|
| Eat salty foods or snacks one or more times a day (%) | 28.5 | 27.4 | 29.8 |
| Eat deep fried foods or snacks or fast foods three or more times a week (%) | 11.2 | 8.8 | 14.2 |
| Eat less than one serving of fruit a day (%) | 14.1 | 11.8 | 16.8 |
| Eat less than one serving of vegetables a day (%) | 6.4 | 5.0 | 8.2 |
| Eat meat and/or poultry two or more times a day (%) | 29.5 | 26.2 | 33.5 |
| No alcohol intake (%)   | 5.8     | 6.8   | 4.5 |
| Depression (%)          | 16.8    | 21.7  | 10.9|
| Home or work stress (%) | 30.7    | 36.8  | 23.2|
| Married or common law (%)| 75.4    | 69.8  | 82.4|
| Employed or retired (%) | 92.7    | 90.1  | 95.9|
| Post-secondary education (%) | 86.8 | 85.8 | 88.1 |
| Social disadvantage score³ | 1.2 (1.3) | 1.3 (1.4) | 1.1 (1.3) |
| High social disadvantage (%) | 6.3 | 8.1 | 4.0 |
| Prevalent cancer (%)    | 6.6     | 7.7   | 5.2 |
| Prevalent non-atherosclerotic CVD (%) | 7.0 | 6.6 | 7.4 |
| INTERHEART risk score   | 10.1 (5.8) | 8.8 (5.4) | 11.7 (5.8) |
| Framingham Risk Score (N = 3889) | 11.7 (4.1) | 11.0 (4.1) | 12.5 (3.9)|

Data are presented as mean (SD) or proportions. Family history of MI indicates if either biological parent has had a MI. Elevated cholesterol is defined by self-reported high cholesterol or those taking cholesterol-lowering statin medication daily. Self-reported diabetes is defined by those with any type of diabetes and on treatment. Hypertension is defined by those on medication for hypertension or those with a baseline SBP >140 mmHg or DBP >90 mmHg. Abdominal obesity is defined for women as a WHR >0.85 and for men as a WHR >0.90. Leisure physical inactivity is a self-reported measure of being mainly sedentary or doing minimal effort exercise during leisure time. Poor diet quality is defined, based on the diet portion of the IHRS, as those with a sub-score greater than two of the possible six demerit points. Depression is self-reported as those who felt sad, blue, or depressed for two consecutive weeks or longer, in the past year. Home or work stress is self-reported as those who had several or permanent stress at work or home in the past year.

³Social disadvantage score was calculated by: income less than $25 000/year assigned a score of 2, income between 25 and 75 000 dollars per year a score of 1, unemployment (including retirement) was assigned a score of 2, and living without a partner was assigned a score of 1. The maximum social disadvantage score was 5, and the lowest possible score was 0, reflecting the least social disadvantage.
Statistical considerations
The CAHHM cohort study has high statistical power for the testing of associations between cardiovascular risk factors and subclinical MRI outcomes. Proportions or means with standard deviations are provided for baseline characteristics, cardiac risk scores, and baseline MRI findings. The trend tests for MRI outcomes between low, moderate, and high-risk categories of risk scores were made using one-way analysis of variance with linear contrasts for continuous outcomes and the Cochran Armitage Trend for bivariate outcomes. Overall and sex-stratified logistic regression models were used to identify the association between a 5-point increase in the IHRS (approximately equal to 1 SD) and each categorical MRI finding (i.e. SBI and IPH) and the continuous measure of CWV. These analyses were then repeated in the subset of participants with the Framingham Risk Score. Neither adjustment for centre nor social disadvantage, defined using a scoring system including employment, income, and marital status, altered the results, and therefore, crude odds ratios are presented. The addition of CWV to the risk scores association with each of the MRI outcomes and the MRI-cerebrovascular composite was performed using multivariate logistic regression.

Results
Between January 2014 and March 2018, 7594 participants free of clinical cardiovascular disease completed a non-enhanced MRI scan and had complete risk factor information collected (Supplementary data online, Figure S1).

Demographic characteristics
The demographic characteristics of the cohort participants are found in Table 1. Briefly, the cohort consisted of 55% women; the average age of participants was 58 years; and 19.6% were non-white. Participants were well educated, and social disadvantage was low (Table 1).

INTERHEART risk score
The mean non-lab-based IHRS was 10.1 (5.8). The frequency of component factors of the IHRS is depicted in Table 1. The proportion of participants who reported current smoking (5.4%) or a diagnosis of

| Table 2  | MRI outcomes by INTERHEART risk score category |
|---------|-----------------------------------------------|
| Number  | Overall 7594 | INTERHEART risk score category |
|         |               | Low risk | Moderate risk | High risk | P-trend* |
| INTERHEART risk score | 10.1 (5.8) | 5.5 (2.6) | 12.2 (1.7) | 19.4 (3.3) |           |
| Framingham Risk Score | 11.7 (4.1) | 9.9 (3.3) | 12.6 (3.8) | 15.3 (3.6) |           |
| Carotid vessel wall volume (mm³) | 902.6 (167.5) | 881.5 (163.1) | 915.4 (166.6) | 940.9 (172.9) | <0.0001 |
| Intraplaque haemorrhage | 2.4% (179/7488) | 1.8% (67/3783) | 3.0% (72/2405) | 3.1% (40/1300) | 0.001 |
| Silent brain infarction | 4.0% (301/7523) | 2.8% (106/3798) | 4.8% (116/2413) | 6.0% (79/1312) | <0.0001 |
| Lacunar | 2.3% (172/7523) | 1.6% (60/3798) | 2.6% (62/2413) | 3.8% (50/1312) | <0.0001 |
| Non-Lacunar | 1.7% (129/7523) | 1.2% (46/3798) | 2.2% (54/2413) | 2.2% (29/1312) | 0.003 |
| MRI-detected cerebrovascular disease | 6.2% (462/7449) | 4.5% (168/3770) | 7.5% (179/2388) | 8.9% (115/1291) | <0.0001 |

Data are presented as mean (SD) or proportions (counts).
IHRS, INTERHEART risk score.
P-trend calculate using linear contrasts for continuous data and Cochran Armitage Test for bivariate outcomes.

| Table 3  | MRI outcomes by Framingham Risk Score category |
|---------|-----------------------------------------------|
| Number  | Overall 3889 | Framingham Risk Score category |
|         |               | Low risk | Moderate risk | High risk | P-trend* |
| INTERHEART risk score | 10.0 (5.7) | 7.1 (4.3) | 11.4 (5.0) | 15.4 (5.2) |           |
| Framingham Risk Score | 11.7 (4.1) | 8.4 (2.4) | 13.4 (1.3) | 17.5 (2.1) |           |
| Carotid vessel wall volume (mm³) | 904.4 (167.4) | 869.2 (152.9) | 924.8 (170.9) | 963.5 (175.9) | <0.0001 |
| Intraplaque haemorrhage | 2.1% (82/3825) | 1.2% (23/1891) | 2.2% (27/1254) | 4.7% (32/680) | <0.0001 |
| Silent brain infarction | 3.6% (138/3860) | 2.1% (39/1902) | 3.5% (44/2413) | 7.9% (55/694) | <0.0001 |
| Lacunar | 2.2% (86/3860) | 1.3% (24/1902) | 2.1% (26/1264) | 5.2% (36/694) | <0.0001 |
| Non-Lacunar | 1.3% (52/3860) | 0.8% (15/1902) | 1.4% (18/1264) | 2.7% (19/694) | <0.001 |
| MRI-detected cerebrovascular disease | 5.6% (212/3814) | 3.2% (61/1887) | 5.5% (69/1247) | 12.1% (82/680) | <0.0001 |

Data are presented as mean (SD) or proportions (counts).
FRS, Framingham Risk Score (modified).
P-trend calculate using linear contrasts for continuous data and Cochran Armitage Test for bivariate outcomes.
diabetes (4.9%) was low, whereas the proportion of participants with hypertension (38.4%), elevated blood cholesterol including those using a cholesterol-lowering statin (36.7%), or abdominal obesity (50.5%: 37.7% female, 66.4% male) was high. Half of the participants (3814/7594) were classified as low risk (score of 0–9, mean 5.5), 32.2% (2445/7594) as moderate risk (score 10–15, mean 12.2), and 17.6% (1335/7594) were classified as high risk (score >_16, mean 19.4).

Framingham Risk Score
In the subset of the participants who provided blood samples, the Framingham Risk Score was calculated. The mean score was 11.7 (4.1); and 49.1% (1912/3889) of participants were classified as low risk, 32.9% (1278/3889) as intermediate, and 18.0% (699/3889) as high risk.

Association between risk scores and subclinical MRI outcomes
The overall frequency of IPH was 2.4% (179/7488) and SBI was 4.0% (301/7523) (lacunar: 2.3%; non-lacunar 1.7%). The proportion of participants with subclinical cerebrovascular disease including IPH or SBI increases progressively from low to moderate, to high risk by the IHRS, as does the mean CWV, with a strongly significant trend statistic for each outcome (Table 2). The proportion of participants with any MRI-detected cerebrovascular disease in the low-risk strata was 4.5%, in moderate risk was 7.5%, and in high risk was 8.9%, P < 0.0001 for the IHRS categories. Similar associations were observed for the Framingham Risk Scores (Table 3) (Figure 1A and 1B).

Each 5-point increase (about 1 SD) in the IHRS was associated with a 23% increase in carotid IPH (95% confidence interval (CI) 9–38%), and a 32% increase in SBI (95% CI 20–45%). A 5-point increase in IHRS has also associated a 29% (20–39%) increase in the odds of MRI-cerebrovascular composite of carotid IPH or SBI (Figure 2A). The Framingham Risk Score which incorporates the lipid measures was also significantly associated with MRI-cerebrovascular disease, including IPH and SBI (Figure 2B). These associations were also consistent by age, sex, racial-ethnic group, and social disadvantage strata (Figure 3).

A 5-point change in IHRS and Framingham Risk Score increases the CWV, a continuous measure of subclinical atherosclerosis, by 9 mm^3 (P < 0.0001) and 11 mm^3 (P = 0.0002), respectively, adjusting for sex. We also tested if the CWV remained significantly associated with MRI-cerebrovascular disease when added to the cardiac risk score. Added to the IHRS, the CWV association with MRI-cerebrovascular disease was independent and additive as was the case for the addition of CWV to the IHRS association with SBI (Table 4). The CWV reduces the magnitude and significance of the IHRS association with IPH (P = 0.07). Added to the Framingham Risk Score, CWV was independently and significantly associated with MRI-cerebrovascular disease, for IPH and SBI (Table 5).

Discussion
We demonstrate in this large population-based cohort of adult men and women that traditional cardiovascular risk factors as measured by simple cardiac risk scores were associated with MRI-detected subclinical cerebrovascular injury including carotid IPH and SBI (both lacunar and non-lacunar). These associations are consistent across the lifespan, in both sexes, in White and non-White individuals, and low- and high-socioeconomic groups. Furthermore, CWV, a measure of positive remodelling and an index of atherosclerosis was independently associated with MRI-detected cerebrovascular disease, demonstrating the potential utility of this imaging biomarker.

Assessment of subclinical vascular injury is a useful adjunct to identify individuals who require risk factor control to prevent the development of clinical events. Our findings add significantly to the body of literature which shows that subclinical vascular disease begins far earlier in life than at the time of clinical presentation of first MI, stroke or death, and that pre-clinical measures of carotid...
Figure 2  (A) Risk of MRI-detected cerebrovascular disease per 5-point increase in the non-lab-based INTERHEART risk score.  (B) Risk of MRI-detected cerebrovascular disease per 5-point increase in the Framingham Risk Score. (A) The odds ratio and 95% confidence interval for each MRI outcome per 5-point increase in the non-lab-based INTERHEART risk score; (B) the odds ratio and 95% confidence interval for each MRI outcome per 5-point increase in the Framingham Risk Score. MRI-detected cerebrovascular outcome defined as intraplaque haemorrhage or silent brain infarction.

Figure 3  Risk of combined MRI-detected cerebrovascular disease per 5-point increase in the non-lab-based INTERHEART risk score in various sub-groups. The risk of MRI-detected CVD per 5-point increase in INTERHEART risk score is shown overall, and within selected subgroups showing consistency of the effect by sex, age group, race, and social disadvantage category (moderate to high defined as points $\geq 3$, low score $<3$).
atherosclerosis predict the development of severe cerebrovascular injury. Three-dimensional MRI to determine CWV and IPH offer a direct and precise measure of the normal and diseased wall and is superior to carotid ultrasound because of its ability to accurately characterize vessel wall plaque biomarkers, including plaque components, plaque burden, and luminal stenosis. MRI is currently the only available clinical imaging technique for the detection of plaque haemorrhage—one marker of a vulnerable plaque in the carotid artery. Other imaging biomarkers which can indicate plaque vulnerability include lipid-rich necrotic core, calcification core, and calcification which were not studied as part of our MRI protocol. CAHHM shows that cardiac risk scores are significantly associated with subclinical atherosclerosis measured by CWV and IPH. Most prior studies using MRI of the carotid arteries have been smaller in size and conducted among higher risk individuals. The Rotterdam cohort study evaluated older individuals (average age 77 years) known to have increased carotid intimal medial thickness by ultrasound, and reported that increasing age, cigarette smoking, and hypertension were associated with the presence of IPH, and that lipid measures were associated with CWV. Furthermore in the Rotterdam cohort increased luminal stenosis of the carotid artery was strongly associated with IPH, and CAHHM shows that a continuous measure of atherosclerosis—carotid vessel wall volume is significantly associated with IPH.

Regarding carotid disease and clinical outcomes, IPH is associated with an increased risk of clinical events including stroke or transient ischaemic attack (TIA) in patients with known carotid stenosis, although studies in asymptomatic individuals are very limited in size. The MESA study in 946 participants with increased carotid intimal medial thickness by ultrasound, showed that an MRI-based vascular remodelling index of the internal carotid artery was associated with incident cardiovascular events over 5 years, and was superior to carotid intimal medial thickness as measured by ultrasound. Our data in a middle-aged population without a history of CVD show that MRI-measured CWV is significantly associated with IPH, and SBI, over and above cardiac risk factors. Prospective follow-up of CAHHM is ongoing in order to quantify the risk of each of these MRI biomarkers to clinical cardiovascular outcomes and mortality.

CAHHM to our knowledge is the first report of a strong association between multicomponent but simple cardiac risk scores and the presence of SBI in a large population-based study. Prior cohort studies which used MRI evaluation of SBI were smaller and were conducted in older populations. These studies showed that increasing age, hypertension, and carotid intimal thickness are risk factors for

### Table 4: Independent association of carotid wall volume measure of atherosclerosis in addition to INTERHEART risk score on MRI cerebrovascular disease

| MRI outcome                                  | N Scans | Odds (95% CI)    | P-value |
|----------------------------------------------|---------|-----------------|---------|
| MRI-detected cerebrovascular disease         | 7304    | 1.22 (1.13–1.32) | <0.0001 |
| IHRS (5-point increase)                      |         |                 |         |
| Carotid wall volume (100 mm³ increase)      |         | 1.30 (1.23–1.37) | <0.0001 |
| Intraplaque haemorrhage                      | 7337    | 1.12 (0.99–1.27) | 0.07    |
| IHRS (5-point increase)                      |         |                 |         |
| Carotid wall volume (100 mm³ increase)      |         | 1.54 (1.43–1.65) | <0.0001 |
| Overall silent brain infarction              | 7304    | 1.28 (1.16–1.41) | <0.0001 |
| IHRS (5-point increase)                      |         |                 |         |
| Carotid wall volume (100 mm³ increase)      |         | 1.15 (1.07–1.22) | <0.0001 |

### Table 5: Independent association of carotid wall volume measure of atherosclerosis in addition to Framingham Risk Score on MRI cerebrovascular disease

| MRI outcome                                  | N Scans | Odds (95% CI)    | P-value |
|----------------------------------------------|---------|-----------------|---------|
| MRI-detected cerebrovascular disease         | 3734    | 1.78 (1.49–2.12) | <0.0001 |
| FRS (5-point increase)                       |         |                 |         |
| Carotid wall volume (100 mm³ increase)      |         | 1.26 (1.16–1.36) | <0.0001 |
| Intraplaque haemorrhage                      | 3742    | 1.47 (1.12–1.94) | 0.006   |
| FRS (5-point increase)                       |         |                 |         |
| Carotid wall volume (100 mm³ increase)      |         | 1.46 (1.31–1.63) | <0.0001 |
| Overall silent brain infarction              | 3734    | 1.98 (1.60–2.46) | <0.0001 |
| FRS (5-point increase)                       |         |                 |         |
| Carotid wall volume (100 mm³ increase)      |         | 1.15 (1.04–1.27) | 0.004   |
SBI. In our study, a 5-point increase in the IHRS was associated with a 32% increase in the relative prevalence of SBI (95% CI 20–45%). Furthermore, this association was consistent for lacunar and non-lacunar infarctions, which are approximately equal in frequency in our study. Compared to the non-lab-based IHRS, the Framingham Risk Score was more strongly associated with SBI [ odds ratio 2.02 (95% CI 1.64–2.50 per 5-point increase)] which may reflect the inclusion of lipid measures, together with the other traditional cardiovascular risk factors. We also show that subclinical atherosclerosis measured by CWV was significantly associated with SBI over and above cardiovascular risk factors. While CAHHM does not yet have follow-up data regarding the risk of clinical stroke, prior studies indicate that persons with silent brain infarcts are at three-fold increased risk of future stroke and 1.5-fold increased risk for dementia.10,35

Our data emphasize that simple cardiac risk scores are useful to risk stratify the population, and clinical trial strategies have directed the use of statins and blood pressure lowering in moderate to high-risk individuals in primary prevention.22 Recent guidelines highlight additional risk stratification markers beyond risk scores may be needed in cases of clinical uncertainty or patient indecision regarding treatment, and endorse additional measures of subclinical atherosclerosis over the use of serum biomarkers.36 While it is impractical to consider MRI for population-based screening, our data reaffirm that non-invasive imaging with MRI is highly informative. In addition to simple cardiac risk scoring, MRI-detected CWV adds additional information regarding subclinical vascular injury of the carotid arteries and brain.

The strengths of our analyses include CAHHM’s large sample size, the use of standard imaging protocols and core lab readings (Supplementary data online, Appendix S3), and the concurrent scanning of multiple vascular territories. Limitations include the cross-sectional nature of our current analysis of the cardiac risk score and MRI-detected cerebrovascular disease, although the chance of reverse causation is low having used subclinical outcomes. Measures of cognitive function have been collected and analysis is underway to determine the relationship between subclinical cerebrovascular disease and cognitive function. The prediction of the cardiac risk scores and MRI-detected cerebrovascular disease on incident clinical events will be reported after prospective follow-up is completed.

Summary
Cardiovascular risk factors summarized as simple risk scores are significantly associated with the presence of MRI-detected subclinical cerebrovascular disease, including CWV, IPH, and SBI in an adult population without known clinical CVD.

Supplementary data
Supplementary data are available at European Heart Journal - Cardiovascular Imaging online.

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Conflict of interest: none declared.

Appendix: CAHHM Investigators and Study Personnel
Steering Committee: S. Anand (Chair), M. Friedrich (Co-Chair), J. Tu (Co-Chair), P. Awadalla (OH), T. Dummer (BCGP), N. Le (BCGP), P. Robson, J. Vena (ATP), S. Jacquemont (CaG), L. Parker (APATH), J.-C. Tardif (MHI Biobank), K. Teo (PURE-Central), and B.-M. Knoppers (ELSI).

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