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Cardiovascular risk scoring and magnetic resonance imaging detected subclinical cerebrovascular disease

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Aims

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 (CWV), 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 CWV, carotid IPH, and SBI was determined. The mean age of the cohort was 58 (8.9) years, 55% were women. Each 5-point increase (~ 1 SD) in the IHRS was associated with a 9 mm³ increase in CWV, adjusted for sex ($P < 0.0001$), a 23% increase in IPH [95% confidence interval (CI) 9–38%], and a 32% (95% 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 CWV, IPH, and SBI. CWV 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 CWV, IPH, and SBI in an adult population without known clinical CVD.

Keywords

magnetic resonance imaging • atherosclerosis • silent brain infarction • risk factors

Introduction

Cardiovascular disease (CVD) is one of the leading causes of death in high-income countries.¹ Risk factors for the two common manifestations of CVD, myocardial infarction (MI) and stroke, have been extensively studied.^{2,3} Over 80% of the risk of these conditions is explained by modifiable risk factors including smoking, abdominal obesity, diabetes, hypertension, and abnormal lipids.⁴ Several simple well-validated cardiovascular scores including non-lab-based risk scores have been proposed to evaluate the risk of developing clinical CVD.^{5–7}

Magnetic resonance imaging (MRI) can accurately measure subclinical manifestations of vascular injury and has been used to identify individuals who have a higher risk of clinical vascular events in several studies in different populations.^{8–13} MRI is superior to computed tomography for diagnosis of silent cerebrovascular disease and does not expose participants to radiation.¹¹ Most prior MRI cohort studies have been conducted in older populations,¹⁴ in which participants were selected for MRI based on increased subclinical carotid disease on ultrasound,^{14–17} and few large population-based studies have evaluated whether simple cardiac risk scores are associated with MRI-detected subclinical cerebrovascular disease including carotid wall volume (CWV), intraplaque haemorrhage (IPH), and silent brain infarction (SBI), subdivided by lacunar and non-lacunar types.¹⁸

In the Canadian Alliance for Healthy Hearts and Minds Cohort Study (CAHHM), we sought to determine if simple cardiac risk scores are associated with MRI-detected carotid artery disease and SBI.

Methods

Research ethics board approval was obtained from each participating centre. All participants signed consent forms prior to beginning in the study. CAHHM is a 'cohort of cohorts' as the majority of participants (>80%) were recruited through existing cohorts as previously described.¹⁹ Participants were eligible for CAHHM if they were between ages 35 and 69 years at the time of screening, and willing to complete questionnaires, and have physical measurements taken, and undergo an

MRI scan of the brain and carotid arteries. Participants were excluded if they had any contraindications to undergoing an MRI scan.¹⁹ Details of the CAHHM MRI protocol have been previously published.¹⁹ Participant recruitment by cohort and magnet strength are provided in [Supplementary data](#) online, *Appendix S1*. Participants of the First Nations cohort also conducted in parallel are not included.²⁰

In order to quantify the cardiovascular risk factor burden, we calculated the non-lab-based INTERHEART risk score (IHRS) using the version that did not include data on lipid levels.^{6,21} The non-lab-based IHRS is a validated score that includes data on age, sex, status with respect to smoking, exposure to second-hand smoke, diabetes, high blood pressure, and family history of MI, waist-to-hip ratio (WHR); home or work social stress, depression; simple dietary questions, and physical activity. Scores range from 0 to 48, with higher scores indicating a greater risk-factor burden. Cardiovascular risk tertiles corresponding to a score of 9 or less were classified as low risk, a score of 10 to 15 classified as medium risk, whereas a score of 16 and higher defined higher-risk subjects.^{6,22} Details concerning the development and validation of the IHRS have been published previously.^{6,7} The questions and scoring system are found in [Supplementary data](#) online, *Appendix S2*. In a subset of participants in whom blood was collected ($n = 3889$) Apolipoprotein A1 and B were measured which allowed calculation of the Framingham Risk Score using age and sex-specific prediction equations; high-density lipoprotein, and total cholesterol were estimated using measured Apolipoprotein B and A1 values.²³ Participants were scored and then categorized into sex-specific risk categories as per the published Framingham Risk Score⁵ ([Supplementary data](#) online, *Appendix S2*).

Key MRI outcomes

The MRI protocol was previously published.¹⁹ Briefly, participants underwent a short non-contrast enhanced scan using a 1.5 or 3 T magnet. Each centre underwent a test scan for quality assurance which was evaluated and validated by the two MRI core labs (brain and carotid) prior to proceeding with recruitment. Details of each MRI outcome assessment and measurements are found in [Supplementary data](#) online, *Appendix S3*.

Brain

Brain infarcts identified on MRI were subcategorized based on location and size as small (≤ 15 mm axial diameter) subcortical lacunes,²⁴ which

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 score ^a	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.

^aSocial 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.

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 2 MRI outcomes by INTERHEART risk score category

Number	INTERHEART risk score category				P-trend ^a
	Overall 7594	Low risk 3814	Moderate risk 2445	High risk 1335	
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 (mm ³)	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.

^aP-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	Framingham Risk Score category				P-trend ^a
	Overall 3889	Low risk 1912	Moderate risk 1278	High risk 699	
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 (1.5)	17.5 (2.1)	
Carotid vessel wall volume (mm ³)	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% (44/1264)	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).

^aP-trend calculate using linear contrasts for continuous data and Cochran Armitage Test for bivariate outcomes.

Statistical considerations

The CAHHM cohort study has high statistical power for the testing of associations between cardiovascular risk factors and subclinical MRI outcomes.¹⁹ 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,²⁶ 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 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		
IHRS (5-point increase)		1.22 (1.13–1.32)	<0.0001
Carotid wall volume (100 mm ³ increase)		1.30 (1.23–1.37)	<0.0001
Intraplaque haemorrhage	7337		
IHRS (5-point increase)		1.12 (0.99–1.27)	0.07
Carotid wall volume (100 mm ³ increase)		1.54 (1.43–1.65)	<0.0001
Overall silent brain infarction	7304		
IHRS (5-point increase)		1.28 (1.16–1.41)	<0.0001
Carotid wall volume (100 mm ³ 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		
FRS (5-point increase)		1.78 (1.49–2.12)	<0.0001
Carotid wall volume (100 mm ³ increase)		1.26 (1.16–1.36)	<0.0001
Intraplaque haemorrhage	3742		
FRS (5-point increase)		1.47 (1.12–1.94)	0.006
Carotid wall volume (100 mm ³ increase)		1.46 (1.31–1.63)	<0.0001
Overall silent brain infarction	3734		
FRS (5-point increase)		1.98 (1.60–2.46)	<0.0001
Carotid wall volume (100 mm ³ increase)		1.15 (1.04–1.27)	0.004

atherosclerosis predict the development of severe cerebrovascular injury.²⁸

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.¹³ 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,²⁹ and calcification³⁰ 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,^{12,31} and that lipid measures were associated with CWV.³² Furthermore in the Rotterdam cohort increased luminal stenosis of the carotid artery was strongly associated with IPH,³² 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,^{31,33} although studies in asymptomatic individuals are very limited in size.³⁴ 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.¹² 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 smaller³⁵ and were conducted in older populations.¹⁷ These studies showed that increasing age, hypertension, and carotid intimal thickness are risk factors for

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 (OHS), 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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N. Konyer, and S. Zafar; (707) G. Paraga and L. Reid; (714) A. Dick and F. Ahmad; (799) D. Kelton and H. Shah; (801) F. Marcotte and H. Poiffaut; (817) M. Friedrich and J. Lebel; (802) E. Larose and K. Bibeau; (913) R. Miller, L. Parker, D. Thompson, and J. Hicks; (1001) J.-C. Tardif and H. Poiffaut; (1103) J. Tu, K. Chan, A. Moody, and V. Thayalasuthan.

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CAHHM Scientific Review Board: Bob Reid, Ian Janssen, Amy Subar, and Rhian Touyz.

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