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Prevalence and Distribution of Atherosclerosis in a Low- to Intermediate-Risk Population

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ABBREVIATED TITLE PAGE

Manuscript title: Prevalence and distribution of atherosclerosis in a low to intermediate risk population: assessment by whole body MR angiography.

Manuscript type: Original Research.

Implications for Patient Care:

1. Whole body magnetic resonance angiography is feasible at a population level and detects early atherosclerotic disease missed by modalities assessing single vascular sites.

2. Early atherosclerotic disease detected by whole body magnetic resonance angiography is scattered throughout the body. Thus early disease would be missed by evaluating only a single vascular territory.

Summary statement: Whole body magnetic resonance angiography identifies early vascular disease at a population level. Its systematic nature allows detection of early atherosclerotic disease that may be missed by assessing single vascular sites.

ABSTRACT

Purpose:

To quantify the burden and distribution of asymptomatic atherosclerosis in a population with a low-intermediate risk of cardiovascular disease.

Materials and Methods:

Between June 2008 and February 2013 1,528 participants with <20% 10-year risk of cardiovascular disease were prospectively enrolled. They underwent whole body magnetic resonance angiography (WBMRA) at 3T using a two injection, 4 station acquisition technique. Thirty-one arterial segments were scored according to maximum stenosis. Scores were summed and normalized for the number of assessable arterial segments to provide a standardized atheroma score (SAS). Multiple linear regression was performed to assess effects of risk factors on atheroma burden.

Results:

1,513 participants (577/1513 (37.9%) male, median 53.5 years old (Range 40-83)) completed the study protocol. Of 46,903 potentially analyzable segments, 46,601 (99.4%) were interpretable. 2,468 segments (5%) demonstrated stenoses, of which 1649 (3.5%) were <50%, and 484 (1.0%) were ≥50% stenosis. Vascular stenoses were distributed throughout the body with no localized distribution. 747 (49.4%) participants had at least one stenotic vessel, and 408 (27.0%) participants had multiple stenotic vessels. On multivariable linear regression, SAS correlated with age (B=3.4, 95% CI 2.61-4.20), heart rate (B=1.23, 95%CI 0.51-1.95), systolic blood pressure (B=0.02, 95% CI 0.01-0.03), smoking status (B=0.79, 95% CI 0.44-1.15) and socioeconomic status (B=-0.06 (95%CI -0.10 - -0.02) (p<0.01 for all).

Conclusion:

Whole body magnetic resonance angiography identifies early vascular disease at a population level. While on a per-vessel level disease prevalence is low, on a per-participant level, vascular disease is common even in this low-intermediate risk cohort.

MAIN BODY

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity causing 30.8% of all deaths in the US (1). Atheroma develops over a period of time and subclinical disease is present for some time before clinical symptoms are noticed (2). Current techniques for early plaque detection such as coronary calcium scoring and carotid intima-media thickness (CIMT) are all currently limited to one cardiovascular territory. Atherosclerosis is, however, a systemic disease affecting the entire body, thus early atherosclerosis may be missed by single site techniques.

Global efforts have been focused on both the ability to use imaging to better understand the interaction between genetics and early disease such as in the UK Biobank imaging substudy which is in the process of scanning 100,000 out of the 500,000 originally enrolled in the overarching UK biobank study (3), but also in the role of whole body imaging as a screening technique at a population level such as in the SHIP (Study of Health in Pomerania) study (4). Contrast-enhanced whole body magnetic resonance angiography (WBMRA) is one such technique allowing a systematic approach to imaging the entire vascular tree to stratify and quantify cardiovascular disease (5-11). Magnetic resonance (MR) angiography has been shown to be highly accurate in detection of stenosis when compared with invasive angiography (12,13), and previous reports have shown global atheroma burden quantified using WBMRA to correlate with cardiovascular risk, the presence of coronary artery disease and both single and recurrent cardiovascular events (14-18). However, to date, WBMRA has not been examined in a large population free from clinically apparent CVD.

We hypothesis that: early disease would be present even in those considered to be at low-intermediate risk for CVD. Therefore, our study's purpose was to quantify the burden and distribution of asymptomatic atherosclerosis in a population with a low-intermediate risk of cardiovascular disease.

Materials and Methods

Our study (**TA**yside **SC**reening **FOR** **C**ardiac **E**vents or TASCFORCE) is a prospective normal volunteer cardiovascular risk screening study (ISRCTN number: ISRCTN38976321). Our protocol was approved by the Tayside Committee of Medical Research Ethics. Written informed consent was obtained from each participant prior to enrollment in our study.

Men and women aged 40 years or older living in Tayside or Fife, Scotland, were eligible for participation. Recruitment was performed using a random cluster sampling pattern with pre planned periodic sample review to ensure the recruited population accurately represented the sex, age and socioeconomic status of the Tayside population from which it was drawn. When deviations from this occurred recruitment strategies were modified to target those groups who were under-represented. Exclusion criteria were: known atherosclerotic disease; predicted increased risk of CVD requiring statin treatment according to the Scottish Intercollegiate Guideline Network, Guideline 97 (17) (risk increased ≥20% in 10 years); blood pressure (BP) greater than 145/90mmHg; diabetes; inability to give informed consent. To produce a cohort able to participate in a potential future statin intervention study, those with a primary muscle disease, biochemical abnormalities, other serious illness or abnormalities that may compromise the participant's safety taking a statin, known alcohol abuse, pregnancy; breast-feeding; women of child-

bearing potential not using adequate contraception or participation in a clinical trial other than observational trials or registries concurrently or within 30 days prior to screening were also excluded. These criteria were examined at visit 1, during which blood was collected for cholesterol measurement in non-fasting conditions (random sample), to allow calculation of both the cardiovascular risk score and brain natriuretic peptide (BNP). Those with diabetes were excluded from the study. If the random blood glucose serum level was >7mmol/l they were excluded from the study and referred to their family practitioner for further work-up. Smoking status was self classified by participants as never smoker, ex smoker or current smoker. The Scottish index of multiple deprivation was calculated based on the home address of the participants used for the calculation of each individual's ASSIGN (ASsessing cardiovascular risk using Scottish intercollegiate guideline network guidelines) score.(19)All participants who took part in the imaging substudy underwent a MR imaging scan at visit 2.

MRI acquisition technique

Cardiac MR and WBMRA were performed at a single center. The imaging protocol for TASCFORCE and the results of the cardiac analysis of 1,515 participants have been previously described (20-23). This is the first report of the vascular analysis for our TASCFORCE imaging study. The scans were performed in an integrated examination on a 32-channel 3T Magnetom Trio (Siemens, Munich, Germany). For the WBMRA, surface coils covering the whole body were placed on each of our study's participants. Unenhanced MR angiography "mask" data were acquired for the thoracic and neck stations and the calf station using a 3D TurboFLASH sequence. 10 ml of 0.5 mmol/ml gadoterate meglumine (Dotarem, Guerbet, France) followed by

20 ml 0.9% sodium chloride were then injected at a rate of 1.5 ml/s. The contrast-enhanced acquisition for station 1 (thoracic and neck vessels) commenced when the contrast agent attained the superior-most aspect at the top of the aortic arch. Post-contrast data for station 4 (the calves) were acquired immediately after completion of station 1, and these were acquired three times consecutively to optimize capture of peak arterial enhancement in both limbs. Following a delay, a 3D Turbo-FLASH "mask" data were acquired for station 2 (abdominopelvic vessels) and station 3 (thigh vessels). The second dose of 15ml of gadoterate meglumine was infused at 1.5 ml/s followed by a 20 ml normal saline flush. Acquisition was triggered when the bolus could be seen arriving in the abdominal aorta. Post-contrast data for station 3 were acquired immediately after completion of the station 2 sequence. The mean time between first and second contrast agent injections was 19 minutes, with a total imaging time of 50 minutes.

WMBRA scoring technique

The MR angiography images were independently analyzed by one of four observers blinded to the clinical characteristics of the study participant (GH 20 years vascular radiology experience, RW 5 years vascular radiology experience, JWM 4 years vascular radiology experience, MAL 2 years vascular radiology experience) using Carestream PACS (v10.1, Rochester, New York, USA) using the original source images, subtracted multiplanar reconstructions and maximum intensity projections. The arterial tree was divided into 31 segments: right and left internal carotid arteries, right and left vertebral arteries, right and left common carotid arteries, innominate artery, right and left subclavian arteries, aortic arch, thoracic aorta, abdominal aorta, celiac trunk, superior mesenteric artery, inferior mesenteric artery, right and left renal

arteries, right and left iliac arteries, right and left femoral arteries (incorporating common and superficial femoral artery), right and left profunda femoris arteries, right and left popliteal arteries, right and left anterior tibial arteries, right and left peroneal arteries, and right and left posterior tibial arteries. Each arterial segment was visually assessed for the region of greatest stenosis. The severity of the stenosis was scored by visually comparing the degree of stenosis compared to the normal diameter of an unaffected part of the vessel on tangential longitudinal views of the vessel using multiplanar reformating. Each segment was coded 0-9 according to the maximum stenosis present within the vessel (codes 0-4) and the presence of aneurysmal dilation (codes 5-9) as per Table 1. For instance a code of zero would represent a completely normal vessel with neither stenosis nor aneurysm, a code of 3 would indicate that the tightest stenosis within the vessel was in the magnitude of 71-99%, and a code 9 would be an aneurysmal occluded vessel. This code was then converted to a final vessel score as per Table 1.

Arterial segments which were not visualized with sufficient clarity for grading of the degree of stenosis were recorded as unassessable. To account for this, the final score was divided by the number of segments which had been successfully analyzed (n), and then calculated as a percentage of the maximum possible stenosis score (see equation below) to produce a 'standardized atheroma score' (SAS) (17). The reproducibility of this scoring technique has been previously reported based on the analysis of 48 scans randomly selected by the trial statistician with excellent intra- and inter-observer agreement (20). See Figure 2 for examples of WBMRAs acquired.

All scans were also separately reviewed and reported for incidental findings by a radiologist (GH or JWM) shortly after being acquired.

Statistical analysis

Data are expressed as mean ± SD for continuous variables, median (range) for ordinal variables and number of participants (%) for nominal variables. Normality tests were performed; if the test failed, when possible, standard transformations were used to generate a Gaussian distribution. The statistical analysis plan was predetermined before data analyses. To compare those who underwent an MR imaging scan with those who did not, a t-test was used for normally distributed variables, Mann-Whitney test for skewed and ranked variables and Chi-square test for binomial variables to test the null hypothesis that samples originate from the same source. Univariable linear regression was used to assess for correlation between the SAS and baseline demographic data in both the whole population and male and females separately. A multivariable linear regression was performed on the whole population with sex accounted for within the model as a dichotomous nominal variable. The model included age, gender, smoking status, systolic BP, diastolic BP, heart rate, total cholesterol, high density lipoprotein cholesterol, LDL cholesterol, triglycerides, body mass index, waist circumference, family history of cardiovascular disease, SIMD decile and BNP level. Those variables with a positively skewed distribution were log transformed to create a near normal distribution. Statistical analyses were performed using computer software R 3.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS v 21 (IBM, New York)). A 2-sided p value of <0.05 was taken to be significant for analyses.

Results

4423 participants were recruited to our TASCFORCE study. Figure 1 summarizes the flow of these participants through our TASCFORCE study. Of the 2047 participants eligible for and offered an MR imaging scan, 373 (18.2%) did not give consent to undergo a scan and 14 (0.6%) failed to attend for their MR imaging scan appointment. 101 participants (4.9%) were not scanned due to claustrophobia (n=83), large body habitus (n=3), problems with intravenous cannulation (13) or other technical issues (n=2). 34 (1.7%) were considered unsafe to undergo a scan due to the presence of metalwork. 74.6% (1528/2047 of those invited) completed or partially completed the scan protocol with 15 (1.0%) excluded due to missing or incomplete data, leaving 1,513 in the final analysis. The characteristics of those who did not complete scanning and those who did have a scan are summarized in table 2.

Incidental findings on MR imaging *scan*

34 participants (2.2% of 1528 participants scanned) had incidental findings on their MR imaging scan which were considered clinically notable by the reviewing radiologists. These included myocardial infarction (n=3); structural cardiac abnormalities (n=7) including cardiomyopathies, septal defects and enlargement of cardiac chambers; benign mass (n=10); malignant mass (n=1); peripheral artery abnormality (n=6) including substantial occlusions or aneurysms; noteworthy anatomical variant (n=5); and others (n=2). These resulted in 16 participants undergoing further downstream testing and 32 undergoing additional review by our study doctor (n=6), their family physician (n=9) or a hospital specialist (n=17) (See supplemental tables S1 and S2 for an overview of the incidental findings and activity resulting from them). Other than these described abnormalities where further follow-

up/intervention were deemed necessary, the findings of the WBMRA were blinded to the patient and their clinicians so as to allow accurate longitudinal assessment of its implications in addition to the lack of proof of intervention currently based on these findings.

WBMRA results

1513 participants were included in the final analysis. A breakdown of the number of arterial segments according to the degrees of luminal stenosis and other abnormalities is illustrated graphically in figure 3. The presence and degree of abnormality is given for each of the 31 segments analyzed per particpant to show the distribution of abnormality. The vast majority of segments (44435/46903, 94.7%) were assessed as normal. Of the vessel segments assessed to have some stenosis or aneurysm, 3.5%(1649/46903) had mild stenosis (<50%), and 1.0% (484/46903) exhibited ≥50% stenosis. 40 arterial segments were aneurysmal although only 7 of these were associated with a stenosis. Therefore, the greatest contribution towards the SASs greater than 0 came from stenoses.

The coeliac trunk was disproportionately affected by stenosis, in addition to which it was also the vessel with the poorest inter-observer repeatability (Fleiss' kappa=0.66 versus ≥ 0.81 in all the other districts) (20). As this stenosis could potentially be either atherosclerotic or secondary to median arcuate ligament compression, the celiac trunk was excluded from the calculation of the SAS score and subsequent analysis.

Despite 94.7% of vessels being normal, 747 (49.4%) out of 1513 participants had at least one stenotic vessel, and 408 participants (27.0%) had stenoses involving multiple arterial segments. At an individual participant level, the number of segments

affected are summarized in figure 4. The distribution of the SAS is illustrated in figure 5 and demonstrate a marked positive skew.

Correlation of WBMRA results with risk factors

The correlations between the SAS and the baseline demographic and risk factors were assessed by univariable analysis (Supplemental table S3). A significant correlation with SAS was present for age ($\rho=0.25$, $p<0.001$), systolic BP ($\rho=0.11$, $p<0.001$), total cholesterol ($\rho=0.16$, $p<0.001$), low density lipoprotein (LDL) ($\rho=0.12$, $p<0.001$), and the adult treatment panel III cardiovascular risk score for both the total population ($\rho=0.15$, $p<0.001$) and for males ($\rho=0.28$, $p<0.001$) and females ($\rho=0.22$, $p<0.001$) separately. Triglycerides showed a correlation for females only, while the Scottish Index of Multiple Deprivation (SIMD) showed a correlation when considered for the whole population, but not when analyzed for each individual gender.

Linear multiple regression modelling demonstrated that age, heart rate, systolic BP, SIMD decile, ex-smoking status and current smoking status were independently associated with SAS (table 3).

Because the SAS was very positively skewed further sensitivity analysis was performed examining both those with a SAS above and below the 80th percentile and the number of stenosed vessels rather than the SAS score. The baseline characteristics of those with a SAS above the 80th percentile are compared with those below the 80th percentile in supplemental table S4. Men and women with an SAS above the 80th percentile were older, had a higher systolic BP and had a higher predicted CHD risk when compared to those with an SAS below the 80th percentile. Additionally, men were more likely to be current or ex-smokers and women had a higher total and LDL cholesterol and higher triglycerides. If, rather than using the

SAS, the number of stenosed vessels was used, or the population was split into those with and without any vascular stenosis, similar results were seen demonstrating the robustness of the observations. (Supplemental tables S5 and S6).

Discussion

Our study shows that within a population considered to be at low-intermediate risk of CVD, that while on a per vessel basis disease prevalence is low at 5.3%, 49.4% of participants 49.4% of participants have at least one vessel with stenotic disease and 27% have multi-vessel disease. This disease is relatively evenly distributed throughout the cardiovascular system.

There was a high technical success rate with only 15 of the 1528 studies (1%) being considered non-diagnostic, demonstrating the aptitude of the technique for more widespread use. Our finding that both the atheroma burden and number of stenotic vessels correlated with age, BP, cholesterol and cardiovascular risk is perhaps unsurprising as these are all risk factors for cardiovascular events (24). We demonstrate a significant association between the global atheroma burden and socioeconomic deprivation, which is in keeping with prior observations of socioeconomic deprivation being a marker of cardiovascular risk (25). Similar associations between socioeconomic status and CIMT have been described in adulthood as well as in children as young as 10, with the exact causative mechanism under debate but is most likely an interplay of stress, second hand smoke and diet.(26,27) These findings provide validation of the atheroma score for the detection of subclinical atherosclerosis in a population not considered to be at high risk for cardiovascular events. Our prevalence of atherosclerotic changes of 49.4% is much lower than the 68% in the PIVUS study (18), however this previous study included

those with known cardiovascular disease and focussed on an older cohort, only recruiting 70 year olds. In contrast, our rates are much higher than the 21% prevalence of vascular disease seen in a previous study in 298 healthy study participants using a variant of the whole-body technique. However, the authors of this previous study only looked for atherosclerotic disease causing greater than 50% stenosis, ignoring lower grade stenoses (7).

While the vast majority of arterial segments in the WBMRAs were normal, almost 50% of the population exhibited pre-clinical stenotic disease, with more than 25% exhibiting multifocal disease. For our study, of the vessels affected by early atherosclerosis, the most common sites detected were the abdominal aorta and iliac arteries. This is of particular interest as both areas are poorly evaluated with current imaging strategies such as coronary calcium scoring or CIMT measurement.

While we have demonstrated the ability of WBMRA to detect extensive subclinical disease, the clinical importance of this is yet to be established, as is the best method for quantifying the extent of atherosclerosis. The PIVUS study showed that the atheroma score was the strongest predictor of major adverse cardiovascular events at 5 years, and improved discrimination and reclassification when added to the Framingham Risk Score, with superior predictive value to CIMT and ankle-brachial pressure index (14). However, the authors did not compare this with the number of diseased vessels. A previous study in those with diabetes mellitus demonstrated that both the atheroma score and the number of diseased vessels conferred prognostic benefits over traditional cardiovascular risk markers (15). Long term follow-up at 5, 10 and 15 years is planned in our TASCFORCE study and will allow us to determine if these observations hold true in a low-intermediate risk cohort, and will also allow comparison of the different metrics of quantifying atheroma development and

distribution to determine whether it is certain vessels, a combination of vessels or a global summation of disease burden that are the best markers of cardiovascular risk. Determination of a particular risk profile of high risk sites may help target other cheaper, more accessible modalities to the relevant vessels, increasing the prognostic yield of these.

Our study has several limitations. WBMRA is a lumenographic technique, thus potentially missing early vascular changes where there is positive remodeling. There are several promising MR imaging techniques for wall thickening and early fatty streak deposition detection (28); yet to date these have only been applied in singular vascular territories with the inherent weaknesses of this as discussed above. In addition the coronary arteries were not assessed. Atheroma burden on WBMRA has previously been demonstrated to correlate well with the presence of obstructive coronary artery disease (29), thus our current results would suggest there was substantial undetected disease within the coronary circulation as well. At the time of our study design, MR coronary angiography was in its infancy, being time consuming, technically challenging, and of limited accuracy; however, recent advances mean it may be incorporated into future whole body angiography. It will be worthwhile to examine the additional disease burden and the prognostic value that this could yield (30).

In conclusion, WBMRA identifies early vascular disease at a population level, and the systematic nature of its evaluation allows it to detect early atherosclerotic disease missed by modalities that only assess single vascular sites.

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Table 1: Coding and scoring for WBMRA arterial segments.

Abnormality	Code	Score*
Normal	0	0
<50% stenosis	1	1
51-70% stenosis	2	2
71-99% stenosis	3	3
Occluded segment	4	4
Aneurysm but no stenosis	5	1
Aneurysm and <50% stenosis	6	2
Aneurysm and 51-70% stenosis	7	3
Aneurysm and 71-99% stenosis	8	4
Aneurysm and occlusion	9	5

The aneurysmal and stenotic status were coded and scored according to the severity of the stenosis. *Score ascribed to contribute to whole body atheroma score. WBMRA=whole body magnetic resonance angiography.

Table 2: Characteristics of those who had an MR imaging scan and those who declined or were unable to complete a scan

Variable	Underwent MR imaging scan (n=1528)	Unable/declined to have MR imaging scan (n=539)	*p value
No (%) men	579 (37.9)	233 (43.3)	0.03
Median (IQR) age (years)	53.5 (12.2)	52.6 (13.3)	0.57
No (%) current smokers	165 (10.8)	57 (10.6)	0.88
No (%) former smokers	417 (27.3)	150 (27.9)	0.81
No (%) never smoked	940 (61.5)	330 (61.3)	0.90
Mean (SD) systolic BP(mmHg)	122.4 (12.1)	123.7 (11.7)	0.046
Mean (SD) diastolic BP(mmHg)	72.8 (9.2)	73.8 (9.3)	0.02
Median (IQR) heart rate (beats per min)	62 (12)	64 (11)	<0.001
Mean (SD) total cholesterol (mmol/l)	5.51 (0.96)	5.51 (1.02)	0.89
Mean (SD) high density lipoprotein (mmol/l)	1.43 (0.42)	1.38 (0.39)	0.04
Mean (SD) low density lipoprotein (mmol/l)	3.39 (0.87)	3.41 (0.93)	0.78
Median (IQR) triglycerides (mmol/l)	1.33 (0.98)	1.41 (0.98)	0.09

Median (IQR) body mass index		26.1 (5.3)	26.3 (6.0)	0.15
Mean (SD) waist circumference (cm)		86.0 (16.0)	87.0 (17.0)	0.10
Median (IQR) CHD risk score		2 (5)	3 (5)	0.19
Median (IQR) ASSIGN score		7.4 (7.9)	7.8 (8.8)	0.18
Number (%) with family history of CV disease		392 (25.7)	128 (23.8)	0.39
SIMD Number (%)	1	65 (4.3)	23 (4.3)	0.14
	2	79 (5.2)	29 (5.4)	
	3	101 (6.6)	50 (9.3)	
	4	77 (5.0)	39 (7.2)	
	5	95 (6.2)	31 (5.8)	
	6	167 (10.9)	40 (7.4)	
	7	248 (16.2)	91 (16.9)	
	8	297 (19.4)	107 (19.9)	
	9	279 (18.3)	92 (17.1)	
	10	117 (7.7)	35 (6.5)	

MR=magnetic resonance, IQR=inter-quartile range, SD=standard deviation, BP=blood pressure, CHD=coronary artery disease, ASSIGN=Assessing cardiovascular risk using Scottish Intercollegiate Guideline Network, CV=cardiovascular, SIMD=Scottish Index of Multiple Deprivation.

*Unpaired t-test was used for normally distributed variables, Mann-Whitney test for skewed and ranked variables and Chi-square test for binomial variables. SIMD was treated as a continuous variable for the purpose of analysis.

Table 3: Multivariable analysis of traditional cardiovascular risk factors, socio-demographic factors and BNP in relation to standardized atheroma score

Risk Factor	B coefficient (95% CI)	P
log age (years)	3.40 (2.61,4.20)	<0.001
log heart rate (bpm)	1.23 (0.51,1.95)	<0.001
log triglycerides (mmol/l)	0.24 (-0.39,0.87)	NS
log BMI (kg/m^2)	-0.26 (-1.46,0.93)	NS
log BNP (pg/ml)	0.15 (-0.08,0.38)	NS
Systolic BP (mmHg)	0.02 (0.01,0.03)	<0.001
Diastolic BP (mmHg)	-0.01 (-0.03,0.01)	NS
Total cholesterol (mmol/l)	-0.12 (-0.95,0.70)	NS
HDL (mmol/l)	-0.01 (-0.87,0.86)	NS
LDL (mmol/l)	0.23 (-0.59,1.04)	NS
Waist circumference (cm)	-0.01 (-0.02,0.01)	NS
SIMD Decile	-0.06 (-0.10,-0.02)	0.005
Male gender (compared to female)	0.05 (-0.25,0.36)	NS
Ex-smoker (v never smoked)	0.35 (0.10,0.60)	0.009
Current smoking (v never smoked)	0.79 (0.44,1.15)	0.004
Family history of CVD (v no family history)	0.24 (-0.01,0.49)	NS
Proportion of variability explained by model§	11.4%	<0.001

§Proportion of variability (adjusted r^2) explained by the cardiovascular, demographic and blood markers included in model. CI=confidence interval, bpm=beats per minute, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure,

HDL=high density lipoprotein, LDL=low density lipoprotein, SIMD= Scottish Index of Multiple Deprivation, CVD=cardiovascular disease.

Figure 1

Participant Flow Diagram of the TASCFORCE Study

Diagram shows participant flow through the study. BNP=brain natriuretic peptide, CV=cardiovascular, MRI=magnetic resonance imaging, WBMRA=whole body magnetic resonance angiography.

Figure 2

Examples of whole body angiograms

Normal study with no disease evident in a 45yo woman (A). Evidence of extensive disease including left carotid bulb stenosis (open arrow head), bilateral renal artery stenosis (closed arrow heads) and an occluded right superficial femoral artery (triangle) in a 53yo woman (B).

Figure 3

Distribution of abnormalities at arterial segment level

The graph shows the incidence of stenoses according to the grade, and of aneurysm.

Total 1= less than 50% stenosis, total 2= 51-70% stenosis, total 3=71-99% stenosis, total 4= occlusion, total >4=presence of aneurysm with or without stenosis. L=left, R=right, ICA=internal carotid artery, VA=vertebral artery, IN AR=innominate artery, CCA=common carotid artery, SC=subclavian artery, AOR A=aortic arch, THOR AO=thoracic aorta, ABD AO=abdominal aorta, COEL=celiac trunk, SMA=superior mesenteric artery, IMA=inferior mesenteric artery, REN=renal artery, ILIAC=iliac

artery, FEM=femoral artery, PROF=profunda femoris artery, POP=popliteal artery,

AT=anterior tibial artery, PER=peroneal artery, PT=posterior tibial artery.

Figure 4

Frequency of stenotic disease

Incidence of stenotic disease according to the number of segments involved, per

participant (celiac trunk excluded).

Figure 5

Standardized atheroma score distribution

Distribution of the standardized atheroma scores in the population (celiac trunk

excluded).

Supplemental table 1: Summary of MR imaging incidental findings requiring clinical review and/or further investigation

Nature of finding	Frequency
Myocardial infarct detected by delayed enhancement	3
Structural cardiac abnormality	7
Benign mass	10
Malignant mass	1
Peripheral arterial abnormality	6
Anatomical variant/malformation	5
Other finding	2

Supplemental table 2: Activity arising as a result of MR imaging incidental findings

Activity	Number of participants
Investigations	
Abdominal/pelvic ultrasound scan	7
Vascular ultrasound scan	2
Plain x-ray	1
Echocardiogram	6
Other investigation*	3
Review	
Review by study doctor	6
Review by General Practitioner	9
Referral and review to hospital specialist	17
Intervention by study team	
Medication started on advice of study doctor	2

*Other investigations include exercise tolerance tests, blood tests.

Supplemental table 3: Univariable analysis of correlations between baseline factors and standardized atheroma score

Variable	Association with SAS		
	Entire population (n=1513)	Men (n=577)	Women (n=936)
Age (years)	0.25 (<0.001)	0.28 (<0.001)	0.23 (<0.001)
Systolic BP (mmHg)	0.11 (<0.001)	0.10 (0.02)	0.13 (<0.001)
Diastolic BP (mmHg)	0.03 (0.19)	0.04 (0.29)	0.04 (0.20)
Heart rate (beats/min)	0.05 (0.05)	0.02 (0.64)	0.06 (0.06)
Total cholesterol (mmol/l)	0.16 (<0.001)	0.13 (0.002)	0.17 (<0.001)
HDL (mmol/l)	0.03 (0.28)	0.00 (0.93)	0.02 (0.49)
LDL (mmol/l)	0.12 (<0.001)	0.10 (0.026)	0.14 (<0.001)
Triglycerides (mmol/l)	0.06 (0.018)	0.05 (0.20)	0.09 (0.007)
BMI (kg/m^2)	-0.03 (0.26)	0.00 (0.92)	-0.03 (0.31)
Waist circumference (cm)	-0.02 (0.43)	0.05 (0.21)	-0.02 (0.47)
SIMD	-0.08 (0.005)	-0.08 (0.06)	-0.01 (0.67)
Predicted CHD risk score using ATPIII algorithm (%/10 years)	0.15 (<0.001)	0.28 (<0.001)	0.22 (<0.001)
BNP (pg/ml)	0.03 (0.20)	0.06 (0.13)	-0.02 (0.64)

Spearman rank correlation test is used. ρ and (p) values are given. SAS=standardized atheroma score, HDL=high density lipoprotein, LDL=low density lipoprotein, BP=blood pressure, BMI=body mass index, BNP=brain natriuretic peptide, SIMD=Scottish Index of Multiple Deprivation, CHD=coronary heart disease, ATPIII= adult treatment panel III.

Supplemental table S4: Baseline variable comparison between those with standardised atheroma score greater and less than 80th centile

Variable	Total population			Men			Women		
	≤80th centile SAS (n=1278)	>80th centile SAS (n=235)	p value	≤80th centile SAS (n=464)	>80th centile SAS (n=113)	p value	≤80th centile SAS (n=786)	>80th centile SAS (n=150)	p value
Median (IQR) age (years)	52.3 (11.8)	58.9 (12.1)	<0.001	51.8 (10.8)	59.9 (10.8)	<0.001	53.4 (8.2)	58.8 (8.2)	<0.001
No (%) current smokers	125 (9.8)	40 (17.0)	0.001	32 (6.9)	19 (16.8)	0.001	90 (11.5)	24 (16.0)	0.12
No (%) former smokers	332 (26.0)	78 (33.2)	0.022	118 (25.4)	45 (39.8)	0.003	205 (26.1)	42 (28.0)	0.61
No (%) never smokers	816 (63.8)	116 (49.4)	<0.001	312 (67.2)	49 (43.4)	<0.001	488 (62.1)	83 (55.3)	0.13
Mean (SD) systolic BP (mmHg)	122.0 (12.1)	125.3 (12.1)	<0.001	124.6 (11.0)	127.2 (10.5)	0.022	120.2 (12.4)	124.3 (12.7)	<0.001
Mean (SD) diastolic BP (mmHg)	72.7 (9.3)	73.5 (9.0)	0.23	74.9 (8.9)	74.8 (8.4)	0.95	71.3 (9.2)	72.8 (9.2)	0.08
Median (IQR) heart rate (beats/min)	62 (12)	63 (13)	0.40	60 (11)	60 (14)	0.73	65 (10)	65 (9)	0.55
Mean (SD) total cholesterol (mmol/l)	5.43 (0.97)	5.71 (0.94)	<0.001	5.38 (0.94)	5.52 (0.78)	0.12	5.46 (1.02)	5.81 (1.02)	<0.001
Mean (SD) HDL (mmol/l)	1.44 (0.42)	1.47 (0.44)	0.35	1.24 (0.39)	1.28 (0.38)	0.39	1.56 (0.40)	1.56 (0.44)	0.98

Mean (SD) LDL (mmol/l)	3.36 (0.88)	3.56 (0.84)	0.001	3.38 (0.85)	3.50 (0.75)	0.15	3.34 (0.90)	3.59 (0.89)	0.002
Median (IQR) triglycerides (mmol/l)$	1.26 (1.00)	1.36 (1.01)	0.043	1.50 (1.22)	1.60 (1.19)	0.95	1.11 (0.84)	1.26 (0.92)	0.002
Median (IQR) BMI (kg/m^2) $	26.2 (5.2)	26.0 (5.4)	0.50	26.7 (4.41)	26.3 (5.19)	0.59	25.6 (5.5)	25.8 (5.5)	0.89
Median (SD) waist circumference (cm)	86.6 (13.1)	86.6 (11.9)	0.99	92.0 (14.0)	93.0 (14.6)	0.72	81.0 (15.0)	82.3 (15.0)	0.55
Median (IQR) predicted CHD risk score using ATPIII algorithm (%/10 years)$	2 (5)	4 (9)	<0.001	6 (6)	10 (5)	<0.001	1 (2)	2 (3)	<0.001
Median (IQR) BNP (pg/ml) $	22.6 (15.0)	23.3 (18.4)	0.19	15.3 (12.0)	16.6 (12.3)	0.07	26.5 (17.3)	26.6 (19.6)	0.90
No (%) with family history of CV disease	323 (25.3)	66 (28.1)	0.37	108 (23.3)	25	0.79	209 (26.6)	47 (31.3)	0.23
SIMD, Number (%) 1	48 (3.8)	17 (7.2)	0.10	12 (2.6)	8 (7.1)	0.31	35 (4.5)	10 (6.7)	0.41
2	66 (5.2)	13 (5.5)		21 (4.5)	4 (3.5)		44 (5.6)	10 (6.7)	
3	80 (6.3)	21 (8.9)		26 (5.6)	10 (8.8)		51 (6.5)	14 (9.3)	
4	66 (5.2)	10 (4.3)		28 (6.0)	6 (5.3)		37 (4.7)	5 (3.3)	
5	80 (6.3)	15 (6.4)		29 (6.3)	6 (5.3)		51 (6.5)	9 (6.0)	

6	143 (11.2)	20 (8.5)		52 (11.2)	13 (11.5)		86 (10.9)	12 (8.0)	
7	202 (15.8)	45 (19.1)		67 (14.4)	21 (18.6)		126 (16.0)	33 (22.0)	
8	254 (19.9)	40 (17.0)		98 (21.1)	18 (15.9)		155 (19.7)	23 (15.3)	
9	231 (18.1)	43 (18.3)		88 (19.0)	20 (17.7)		140 (17.8)	26 (17.3)	
10	105 (8.2)	11 (4.7)		43 (9.3)	7 (6.2)		58 (7.4)	8 (5.3)	

Unpaired t-test used to compare means for variables with a normal distribution.

Mann-Whitney test used for variables with a skewed distribution (indicated by $).

SAS=standardised atheroma score, IQR=interquartile range, SD=standard deviation,

HDL=high density lipoprotein, LDL=low density lipoprotein, BMI=body mass index,

CHD=coronary heart disease, ATPIII= Adult Treatment Panel III, BNP= B-type

natriuretic peptide, CV=cardiovascular, SIMD=Scottish index of multiple deprivation.

Supplemental table S5: Univariable correlations between percentage of arterial segments with any degree of stenosis or aneurysm and baseline risk factors

Variable	Association with percentage of vessels affected by stenosis and/or aneurysm		
	Entire population (n=1513)	Men (n=577)	Women (n=936)
Age (years)	0.26 (<0.001)	0.29 (<0.001)	0.24 (<0.001)
Systolic BP (mmHg)	0.11 (<0.001)	0.10 (0.020)	0.14 (<0.001)
Diastolic BP (mmHg)	0.04 (0.17)	0.03 (0.43)	0.05 (0.13)
Heart rate (beats/min)	0.05 (0.041)	0.02 (0.67)	0.07 (0.043)
Total cholesterol (mmol/l)	0.16 (<0.001)	0.13 (0.001)	0.18 (<0.001)
HDL (mmol/l)	0.03 (0.20)	0.01 (0.82)	0.03 (0.38)
LDL (mmol/l)	0.13 (<0.001)	0.10 (0.027)	0.15 (<0.001)
Triglycerides (mmol/l)	0.06 (0.012)	0.06 (0.13)	0.09 (0.006)
BMI (kg/m^2)	-0.03 (0.30)	0.003 (0.94)	-0.03 (0.32)
Waist circumference (cm)	-0.02 (0.52)	0.06 (0.16)	-0.02 (0.50)
SIMD	-0.04 (0.11)	-0.08 (0.07)	-0.02 (0.58)
Predicted CHD risk score using ATPIII algorithm (%/10 years)	0.15 (<0.001)	0.29 (<0.001)	0.22 (<0.001)
BNP (pg/ml)	0.04 (0.13)	0.07 (0.09)	-0.01 (0.70)

Spearman rank correlation test is used. ρ and (p) values are given. BP=blood pressure, HDL=high density lipoprotein, LDL=low density lipoprotein, BMI=body mass index, SIMD=Scottish index of multiple deprivation, CHD=coronary heart disease, ATPIII= Adult Treatment Panel III, BNP=B-type natriuretic peptide.

Supplemental table S6: Comparison of baseline characteristics between those with no atheroma and those with any atheroma

Variable	Total population			Men			Women		
	No stenosis (n=765)	Any stenosis (n=748)	p value*	No stenosis (n=308)	Any stenosis (n=269)	p value*	No stenosis (n=457)	Any stenosis (n=479)	p value*
Median (IQR) age (years)	51.7 (11.6)	55.3 (13.0)	<0.001	51.5 (10.3)	55.6 (13.5)	<0.001	51.9 (12.3)	55.3 (12.9)	<0.001
No (%) current smokers	68 (8.9)	97 (13.0)	0.010	20 (6.5)	31 (11.5)	0.034	48 (10.5)	66 (13.8)	0.12
No (%) former smokers	199 (26.0)	211 (28.2)	0.32	76 (24.7)	87 (32.3)	0.041	123 (26.9)	124 (25.9)	0.75
No (%) never smokers	496 (64.8)	436 (58.3)	0.011	211 (68.5)	150 (55.8)	0.002	285 (62.4)	286 (59.7)	0.45
Mean (SD) systolic BP(mmHg)	121.6 (12.3)	123.4 (11.9)	0.006	124.6 (11.3)	125.8 (10.5)	0.17	119.7 (12.5)	122.0 (12.4)	0.005
Mean (SD) diastolic BP(mmHg)	72.6 (9.4)	73.0 (9.0)	0.36	74.5 (9.1)	75.2 (8.5)	0.36	71.3 (9.4)	71.8 (9.0)	0.38
Median (IQR) heart rate (bpm)	61 (11)	63 (11)	0.08	60 (12)	61 (12)	0.51	63 (10)	64 (12)	0.14
Mean (SD) total cholesterol (mmol/L)	5.33 (0.93)	5.62 (1.00)	<0.001	5.31 (0.91)	5.52 (0.91)	0.006	5.35 (0.94)	5.67 (1.04)	<0.001
Mean (SD) high density lipoprotein (mmol/l)	1.43 (0.42)	1.45 (0.43)	0.25	1.26 (0.39)	1.24 (0.38)	0.61	1.54 (0.40)	1.57 (0.41)	0.27

Mean (SD) low density lipoprotein (mmol/l)		3.28 (0.85)	3.49 (0.89)	<0.001	3.33 (0.84)	3.48 (0.82)	0.040	3.25 (0.85)	3.51 (0.93)	<0.001
Median (IQR) triglycerides (mmol/l)		1.25 (1.00)	1.30 (1.02)	0.12	1.48 (1.19)	1.60 (1.24)	0.15	1.11 (0.86)	1.17 (0.86)	0.15
Median (IQR) body mass index (kg/m^2)		26.4 (5.3)	26.0 (5.1)	0.16	26.7 (4.3)	26.7 (4.7)	0.80	25.7 (6.0)	25.5 (5.4)	0.10
Mean (SD) waist circumference (cm)		86.9 (13.2)	86.3 (12.6)	0.40	92.0 (11.8)	93.3 (11.0)	0.17	83.4 (13.0)	82.4 (11.7)	0.21
Median (IQR) 10 year CHD risk estimation (%)		2 (4)	2 (5)	<0.001	6 (6)	8 (7)	<0.001	1 (2)	1↑ (2)	<0.001
No (%) with family history of CV disease		188 (24.6)	201 (26.9)	0.31	69 (22.4)	64 (23.8)	0.69	119 (26.0)	137 (28.6)	0.38
SIMD, Number (%)	1	31 (4.1)	34 (4.5)	0.65	8 (2.6)	12 (4.5)	0.31	23 (5.0)	22 (4.6)	0.87
	2	37 (4.8)	42 (5.6)		12 (3.9)	13 (4.8)		25 (5.5)	29 (6.1)	
	3	55 (7.2)	46 (6.1)		20 (6.5)	16 (5.9)		35 (7.7)	30 (6.3)	
	4	37 (4.8)	39 (5.2)		18 (5.8)	16 (5.9)		19 (4.2)	23 (4.8)	
	5	46 (6.0)	49 (6.6)		19 (6.2)	16 (5.9)		27 (5.9)	33 (6.9)	
	6	90 (11.8)	73 (9.8)		38 (12.3)	27 (10.0)		52 (11.4)	46 (9.6)	
	7	113 (14.8)	134 (17.9)		36 (11.7)	52 (19.3)		77 (16.8)	82 (17.1)	
	8	151 (19.7)	143 (19.1)		63 (20.5)	53 (19.7)		88 (19.3)	90 (18.8)	
	9	145 (19.0)	129 (17.2)		63 (20.5)	45 (16.7)		82 (17.9)	84 (17.5)	
	10	57	59		31	19		26	40	

		(7.5)	(7.9)		(10.1)	(7.1)		(5.7)	(8.4)	

*Unpaired t-test was used for normally distributed variables, Mann-Whitney test for skewed and ranked variables and Chi-square test for categorical variables. SIMD was treated as a continuous variable for the purpose of analysis. IQR=inter-quartile range, SD=standard deviation, BP=blood pressure, bpm=beats per minute, CHD=coronary heart disease, CV=cardiovascular, SIMD=Scottish Index of Multiple Deprivation.